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Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function

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This guideline replaces 'Note for guidance on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function' (CHMP/EWP/225/02).

Comments should be provided using this template. The completed comments form should be sent to PKWP@ema.europa.eu

Keywords	***pharmacokinetics, renal impairment, renal function, renal elimination capacity, kidney, elimination, phase I, glomerular filtration rate, GFR, end-stage renal disease, dialysis, metabolite, SmPC***

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Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function

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Executive summary

As patients with renal impairment are often excluded from the pivotal studies establishing efficacy and safety of a new medicinal product, pharmacokinetic data should be used to determine the effect of decreased renal function on drug exposure and to guide dosing recommendations in patients who have altered renal function compared with the pivotal study population. The need to perform a pharmacokinetic study in subjects with decreased renal function and the design and conduct of such a study depend on the characteristics and intended use of the drug under investigation. The development of dosing recommendations should be based on the change in drug exposure or plasma concentrations at decreased renal function as well as on the pharmacokinetic/pharmacodynamic relationship for the drug.

Main changes in the current revision include strengthening of the advice to study the effect of reduced renal function on drugs that are primarily hepatically eliminated and accentuation of the recommendation to use an accurate method for determination of glomerular filtration rate (GFR) in the study subjects. In addition, clarifications have been given and/or minor revisions have been made in most sections of the guideline.

1. Introduction (background)

Pharmacokinetic studies can be used to estimate drug exposure in subpopulations of patients with characteristics that might affect the pharmacokinetics of the drug, and alternative dosing regimens may be developed based on the degree of change in exposure and the pharmacokinetic/pharmacodynamic (PK/PD) relationship. Pharmacokinetic data can, thus, be used to extrapolate efficacy and safety data from the phase III population to subpopulations that were not sufficiently represented in the phase III study. Alternatively, pharmacokinetic data obtained before phase III may be used to allow inclusion of a sub-population in the phase III study.

Renal elimination capacity can be decreased either through renal disease or as a consequence of ageing. Renal impairment has not only been associated with decreased renal excretion of drugs and metabolites but also with changes in absorption, in metabolism and active transport in the kidney, liver or gut, in plasma protein binding and in distribution, especially in patients with severely impaired renal function. Effects of severe renal disease on non-renal elimination mechanisms have been suggested to be attributed to accumulation of uremic factors that inhibit or suppress metabolising enzymes and transport proteins. Renal impairment may also alter the exposure-response relationship for a drug.

2. Scope

It is the objective of this guidance to make recommendations regarding:

- In what situations studies of pharmacokinetics should be performed in subjects with decreased renal function and in patients on dialysis treatment
- The design and conduct of pharmacokinetic studies in subjects with decreased renal function
- Data analysis, presentation and evaluation of results of such studies, including development of dosing recommendations
- Reflection of these results in the SmPC.

3. Legal basis and relevant guidelines

This Guideline should be read in conjunction with Directive 2001/83/EC, as amended, and other relevant pertinent elements outlined in current and future EU and ICH guidelines and regulations. especially those on:

Guideline on reporting the results of population pharmacokinetic analysis [CHMP/EWP/185990/06]).

Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population [CHMP/EWP/14701372004].

Guideline on the investigation of medicinal products in the term and preterm neonate [EMEA/536810/2008].

Guidance on the Summary of Product Characteristics in the Notice to Applicant, Volume 2C.

4. Deciding whether to conduct a pharmacokinetic study in patients with decreased renal function

In the following, the term drug generally refers to the parent compound, while major active metabolites, or clinically relevant active metabolites, are defined as pharmacologically active metabolites estimated to contribute significantly to the total target pharmacodynamic activity, i.e. to an extent that alteration of the exposure to the metabolites might affect overall efficacy and safety.

A pharmacokinetic study in patients with decreased renal function should be conducted for most small-molecule drugs that are intended for repeated administration or continuous infusion, also when the drug/major active metabolite is not primarily eliminated by the kidneys. For a drug intended for a single or occasional administration, a study in subjects with decreased renal elimination capacity should be considered if a prolonged elimination of the drug/active metabolite is a safety concern.

If the drug is expected to be administered to patients on dialysis treatment and if dialysis treatment is expected to influence the pharmacokinetics of the drug/major active metabolite, evaluation of the influence of dialysis treatment on the pharmacokinetics is also recommended. This is further discussed in section 5.5.

If no study is performed in subjects with decreased renal elimination capacity, a justification should be given. In such cases, the Applicant should discuss the risk for effect of decreased renal function on the pharmacokinetics (of parent drug, active and “inactive” metabolites) and should include relevant information in the SmPC (see also section 7). Lack of data may lead to restriction in the use (warnings or contraindications).

Situations when lack of a study in patients with decreased renal function may be justified include:

- hepatically eliminated drugs for which safety data are available indicating that dose adjustments are not necessary even at a markedly increased exposure of the drug and/or its active or toxic metabolites (see also 6.2) or for which treatment can be initiated at a low (safe) dose followed by up-titration of the dose based on relevant markers for efficacy and/or tolerability
- drugs/major active metabolites that are eliminated primarily via the pulmonary route
- large proteins that are not expected to undergo glomerular filtration (e.g. molecular weight >60 kDa), such as monoclonal antibodies
- topically administered drugs without relevant systemic absorption.

A study in subjects with decreased renal elimination capacity may also be exempted in case both the following criteria are fulfilled: the drug cannot be administered to volunteers for safety reasons and the patient population is too small to allow recruitment for a reasonably sized study.

Timing of study

When a posology adjustment is likely to be needed in patients with decreased renal elimination capacity, conduct of a study to evaluate the pharmacokinetics in these patients before phase III should be considered, if possible. In these cases, information on influence of decreased renal elimination capacity on the pharmacokinetics of a drug is valuable when designing the phase III programme, in order to avoid restricting the inclusion/exclusion criteria more than needed and, when possible, be able to give appropriate dosage recommendations in patients with decreased renal function.

5. Study design

The primary goal of a study in patients/subjects with decreased renal function is to determine if the pharmacokinetics of a drug or an active metabolite is altered to such an extent that the dosage should be adjusted from that established in the pivotal efficacy and safety trials.

If renal excretion and/or renal metabolism of the drug or of a clinically relevant active metabolite accounts for about 1/3 or more of the total elimination of the drug/metabolite, a study in patients/subjects with decreased renal elimination capacity should preferably have a “full-range study design” (see section 5.1). A reduced or staged study design as defined below could also be acceptable.

If renal elimination (excretion and renal metabolism) is a minor route of elimination of the drug and active metabolite, a reduced or staged study design may be applicable. A reduced study should be designed to evaluate the worst-case effect of decreased renal function. If the results of a reduced study confirm that severe renal impairment does not alter the pharmacokinetics of a non-renally eliminated drug to a clinically relevant extent, no further study is warranted. If, based on the effect of severe renal impairment on drug exposure (or another relevant pharmacokinetic parameter, see section 6.2), a risk for a clinically relevant difference in pharmacokinetics also at other degrees of renal impairment cannot be excluded additional study groups should be included (staged design). Given that a reduced-design study will necessarily be a small-size study, the Applicant needs to carefully consider *a priori* which strength of evidence that may be obtained and how data should be handled in the decision-making procedure. The change in pharmacokinetics that can be expected to be clinically relevant should be prospectively defined and should, if possible, be justified on the basis of concentration-response relationship of the parent drug and/or its metabolites. Criteria for when the study does not need to be expanded could e.g. be based on confidence intervals, possibly one-sided and/or with a lower confidence level in order to increase the possibility to draw a statistical conclusion. The chosen criteria and the significance level should be pre-specified and carefully justified.

5.1. Study population

For diagnosis, prognosis and treatment of renal disease, the degree of renal impairment is generally categorised based on body size-adjusted glomerular filtration rate (GFR) in ml/min/1.73 m^2. However, in terms of clearance of renally filtrated drugs, the renal elimination capacity is related to absolute GFR in ml/min.

Although renal excretion of a drug may involve tubular secretion as well as glomerular filtration, it is considered sufficient to use GFR as a global measure of renal function in the pharmacokinetic study, also for secreted drugs.

For practical reasons, renal function groups are in this guideline defined as outlined in Table 1, i.e. an absolute GFR< 90 ml/min is defined as decreased renal elimination capacity regardless of e.g. the age or body size of the subjects. The term 'control group' is used for the group best representing renal elimination capacity in the typical patient population for the drug to be studied (phase III population).

It may not be feasible to conduct the study in patients with the condition for which the drug is intended. An acceptable alternative is to use volunteers with different degrees of renal function. In either case, a wide range of renal elimination capacity enhances the ability to detect and characterise the effect of renal function on the pharmacokinetics.

A full-range study should, if feasible, include subjects covering the full renal function range from end-stage renal disease (ESRD) to normal renal elimination capacity (Table 1). If the control group has decreased GFR, a group with normal renal elimination capacity should still be included to evaluate whether an increased dose may be indicated in patients with better renal function than the typical patient.

Renal elimination capacity in included subjects should be assessed using measured GFR (see section 5.2). As individual renal clearance of a filtrated drug is related to absolute and not body surface area-adjusted GFR, absolute GFR should be used to characterise the study groups and at analysis of data (see section 6).

Table 1. Renal function groups

Group	Description	GFR (ml/min)
1	Normal renal elimination capacity	≥ 90
2	Mildly decreased renal elimination capacity	60-89
3	Moderately decreased renal elimination capacity	30-59
4	Severely decreased renal elimination capacity	15-29
5	End stage renal disease (ESRD)	<15 or requiring dialysis treatment

A reduced study of a non-renally eliminated drug should aim at evaluating a worst-case situation in terms of e.g. inhibition/suppression of hepatic metabolism/transport by uremic factors. The study should include two groups, a test group and a control group. The test group should preferably include subjects with as low GFR as possible but not on dialysis treatment, as they would be expected to have the largest accumulation of uremic factors. If inclusion of such patients is not possible, subjects with severely decreased renal elimination capacity (GFR 15-29 ml/min) may be included. However, it should be ascertained that they also have severe renal disease (GFR 15-29 ml/min/1.72 m^2). The control group should represent renal function in the typical patient population for the drug to be studied (phase III population). If the results of a reduced study indicate that also other degrees of renal impairment may alter the pharmacokinetics of the study drug to a clinically relevant extent, other renal function groups should be added to the study (staged study). The decision which groups to add should be based on which other degrees of decreased renal function that, based on the effect in severe renal impairment, could be expected to affect the pharmacokinetics of the study drug.

In the specific situation where certain degrees of renal impairment may not be indicated or will be contra-indicated for other reasons than pharmacokinetics, the study may include only the degrees of renal function that are therapeutically indicated.

For full-range as well as reduced or staged study designs, the included subjects should have chronic renal disease and/or stable renal function. The renal function groups should preferably be comparable

with respect to factors that are expected to significantly influence the pharmacokinetics of the drug. Depending on the characteristics of the specific drug, these may be e.g. demographic factors such as age, gender, weight, or pharmacogenetic factors. Approximately equal numbers of subjects from each of the renal function groups should be recruited to ensure adequate representation. Within each renal function group, the subjects should preferably be chosen to cover the full GFR range. It is particularly important to aim for representation at the lower GFR values in the severe renal impairment group.

For a full-range study, aiming at describing the relationship between renal function and drug clearance, inclusion of e.g. 6-8 subjects per group is usually sufficient. It is acknowledged that a reduced-design study will likely need to be a small-size study and, as outlined above, the Applicant should carefully consider the study size and which statistical criteria can be set in order to decide whether the study should be expanded to include other renal function groups. If a reduced-design study is expanded to include other renal function groups (staged design) the number of subjects in the additional groups may be 6-8 per group.

5.2. Measures of renal function

Renal function is usually assessed by measuring glomerular filtration rate (GFR). The gold standard for assessment of kidney function is a measured GFR using an exogenous substance as a filtration marker (e.g. inulin, ^{51}Cr-EDTA, ^{99m}Tc-DTPA, iothalamate, iohexol). The most adequate dosing recommendations in renal impairment will be developed by using a validated method for measuring GFR. Methods for estimating GFR using endogenous markers have drawbacks and are not as accurate as measured GFR. Furthermore, at time of revision of this guideline, the methods for estimation of GFR (or other estimates of renal function such as creatinine clearance) in clinical practice vary between and within EU member states and over time. Therefore, it is recommended that a method accurately measuring GFR using an exogenous marker is used in pharmacokinetic studies in subjects with decreased renal function.

In addition to measured GFR, presentation and modelling of data (see section 6.3) should preferably be made also using estimated GFR, e.g. from serum creatinine (by e.g. the MDRD or CKD-EPI formulas) or from Cystatin C, or an estimation of creatinine clearance (by e.g. the Cockcroft-Gault formula; see 6.2 Presentation of data and development of dosing recommendations).

GFR should be measured and expressed as ml/min. Dose adjustment in decreased renal function should be based on the subject's absolute GFR and not on a GFR adjusted to body surface area (BSA) of 1.73 m^2. Hence for formulas providing BSA-adjusted GFR (ml/min/1.73 m^2) this should be recalculated to the absolute GFR in ml/min in each individual.

Other measures of renal function that can provide differential characterisation of impairment of glomerular filtration and renal tubular secretion, respectively, may yield additional mechanistic understanding of the effect of decreased renal elimination capacity on the pharmacokinetics. Such methods are encouraged as useful additions in studies in subjects with decreased renal function.

5.3. Drug administration

If the drug and its active metabolites are expected to exhibit dose-linear and time-independent pharmacokinetics also at renal impairment, and steady state pharmacokinetics can be predicted from single-dose data, a single-dose study is sufficient. In single-dose studies, the same dose can in most cases be administered to all subjects in the study, regardless of renal function, since the peak concentration is generally not greatly affected by renal function.

If steady state pharmacokinetics of the drug or an active metabolite cannot be predicted from single-dose data due to non-linear pharmacokinetics, a multiple-dose study is desirable. If possible, the doses in a multiple-dose study should give drug concentrations that are within the clinical therapeutic concentrations range. For multiple-dose studies, lower or less frequent doses may be needed to prevent accumulation of drug and/or metabolites to unsafe levels in subjects with reduced renal function. The duration of dosing should in general be long enough to achieve a steady state. A loading dose strategy may be suitable to facilitate this, particularly if the elimination half-life is greatly prolonged in subjects with decreased renal elimination capacity. If a multiple-dose study is not feasible, e.g. for safety reasons, the Applicant should carefully discuss whether conclusions on dosing recommendations can be drawn from single-dose data, taking degree of non-linearity and therapeutic index of the drug into account.

5.4. Sample collection and analysis

Plasma (or whole blood, as appropriate, and optionally urine) samples should be analysed for parent drug and any major metabolites with known or suspected activity (therapeutic or adverse). Metabolites that are excreted by the renal route will accumulate in patients with decreased renal elimination capacity. Also minor active/toxic metabolites and metabolites that are considered relatively inactive in patients with normal renal function may reach active/toxic levels if the accumulation of the metabolites is substantial. Hence, evaluation of inactive and minor active/toxic metabolites should be considered if they are predominantly eliminated via the kidney and if decreased renal elimination capacity is expected to increase their exposure to levels above those that have been toxicologically qualified.

For renally eliminated drugs, the half-life of parent and metabolites is expected to be prolonged with decreased renal elimination capacity, which needs to be taken into account when determining the duration of sampling. The frequency and duration of plasma sampling and urine collection should be sufficient to accurately estimate relevant pharmacokinetic parameters for the parent drug and metabolites.

If the drug or metabolites exhibit a relatively high extent of plasma protein binding or concentration-dependent protein binding in the therapeutic concentration range, the pharmacokinetics should be described and analysed with respect to the unbound concentrations of the drug and active metabolites in addition to total concentration. If plasma protein binding is concentration-dependent, unbound concentrations should be determined at as many plasma sampling time points as possible, preferably covering high as well as low plasma concentrations. In cases where plasma protein binding has been shown to be independent of concentration, it is sufficient to measure protein binding at one or two time points post-dose and use the determined unbound fraction to calculate unbound exposure. If it is not technically possible to determine protein binding *ex vivo*, an alternative could be an assessment of the effect of pre-dialysis plasma (plasma taken from a dialysis patient shortly before dialysis treatment) or plasma from ESRD patients not yet on dialysis treatment on plasma protein binding *in vitro*, as a worst-case assessment. If no change in *in vitro* protein binding is observed in pre-dialysis plasma, evaluation of unbound exposure in the pharmacokinetic study is not needed.

5.5. Dialysis

The guidance in sections 5.2-5.4 generally applies also to patients with dialysis treatment. Some additional aspects of studying these patients are discussed below.

Dialysis treatment may significantly alter the pharmacokinetics of drugs. For drugs that may need to be administered to ESRD patients undergoing dialysis treatment and where the drug or active metabolites are likely to be extracted during dialysis to such an extent that supplementary dosing after

dialysis treatment may be required, pharmacokinetic evaluation of the contribution of dialysis treatment to the elimination of the drug and potentially active metabolites in ESRD patients is recommended.

Evaluation of plasma pharmacokinetics of the study drug should be made both at drug administration pre-dialysis and at administration post-dialysis i.e. under both dialysis and non- dialysis conditions. Dialysate should be collected in order to determine amount extracted during dialysis treatment.

Primary questions to be addressed are whether the dosage regimen should be adjusted as a consequence of dialysis treatment. The results of the study also provide valuable insight regarding the value of dialysis for treatment of overdose. The assessment of pharmacokinetics in patients on dialysis treatment may be integrated with the pharmacokinetics in the decreased renal function study, as described above.

Intermittent haemodialysis is usually the most important method to be evaluated, as it is the most commonly used in ESRD patients. Pharmacokinetic studies should, however, also be considered in patients on other dialysis regimens such as ambulatory peritoneal dialysis and continuous renal replacement therapy (CRRT) if the drug is likely to be used in such patients. In case pharmacokinetic studies are lacking for peritoneal dialysis or CRRT, and these regimens may be expected to be used in the intended target population, the Applicant should attempt to provide appropriate dosing recommendations based on available data (e.g. data from intermittent haemodialysis, data from similar drugs and measures of dialysis adequacy such as Kt/V, standardised Kt/V and Urea Reduction Ratio). It is, however, noted that extrapolation of the effect of intermittent haemodialysis on the pharmacokinetics of drugs to other dialysis regimens may be difficult.

A drug may not be expected to be largely affected by dialysis if it has high protein binding, a large volume of distribution or a high non-renal clearance, and for such drugs a study in patients on dialysis is not necessary.

5.6. Population pharmacokinetic analysis of sparse data

Based on regulatory experience at time of revision of this guideline, population pharmacokinetic analysis of sparse data has for several renally eliminated investigational drugs underestimated the effect of decreased renal elimination capacity compared with the results of the phase I renal study. The reason for this observation is unclear. Hence, if evaluation of effects of renal function on an investigational drug is indicated (see section 4), a phase I study should be conducted, if possible.

Only if a conventional study with rich data in subjects with decreased renal elimination capacity is not feasible (which should be justified), a population pharmacokinetic analysis of sparse data could be used as an alternative. A population pharmacokinetic analysis replacing a conventional study in decreased renal elimination capacity should be pre-planned and should include a sufficient number of patients and a representative range of renal function so that the study could detect relevant pharmacokinetic differences. As the relationship between renal function and drug clearance might not be the same over the full range of renal function, results of the population analysis should not be extrapolated outside the studied range. Simulation-based analysis of the study design with respect to power to detect an effect of decreased renal elimination capacity is recommended. In cases where levels of parent drug as well as of potentially active/toxic metabolites and/or unbound concentrations are of importance, these would need to be analysed.

Obtaining a measurement of GFR using gold standard methods is likely not feasible in the phase II/III patients included in a population pharmacokinetic analysis. An acceptable alternative for determining renal elimination capacity in population analyses is estimation of GFR e.g. from serum creatinine and

demographic data. Preferably, renal elimination capacity should be estimated repeatedly during the study and as close in time as possible to the pharmacokinetic sampling timepoints. Renal elimination capacity could then be handled as a time-varying factor in the analysis.

The population pharmacokinetic analysis should be performed according to well-established scientific knowledge, the model should be qualified in relation to its purposes (e.g. predictive properties for the different sub-populations and analysis of precision using adequate methods) and the analysis needs to be reported appropriately (see Guideline on reporting the results of population pharmacokinetic analysis [CHMP/EWP/185990/06]).

The uncertainty in the estimated effect of decreased renal elimination capacity (95% confidence intervals) should be determined by adequate methods, preferably using methods not assuming symmetrical distribution of the confidence interval, e.g. bootstrapping or log-likelihood profiling.

5.7. Physiologically-based pharmacokinetic modelling (PBPK)

At time of revision of this guideline, the experience of using PBPK to predict the effect of decreased renal elimination capacity on drug elimination is limited. However, the field of PBPK is evolving and it is foreseen that PBPK modelling may become useful for predicting effects of decreased renal elimination capacity on drug disposition, in particular for drugs that are predominantly renally eliminated. When more knowledge on the effect of renal impairment on e.g. drug metabolism, transport and protein binding has been gained, it may become possible to use PBPK also for non-renally eliminated drugs.

5.8. Pharmacodynamic assessments

The pharmacodynamics could be altered in renal impairment, which could lead to an altered PK/PD relationship. If that is the case, information regarding the PK/PD relationship in renal impairment or information regarding the effect of renal function on relevant biomarkers for efficacy and safety may be important for appropriate evaluation and development of dosing recommendations. Therefore, when possible, it is recommended that assessment of biomarkers for efficacy and/or safety is included within the specific pharmacokinetic study in subjects with decreased renal function. This is especially relevant when the mechanism of action is known to be related to the renal function.

6. Data analysis

The primary intent of the data analysis is to assess whether posology adjustment is required for patients with decreased renal function, and, if so, to develop dosing recommendations based on measures of renal function. The data analysis includes:

- Estimation of pharmacokinetic parameters
- Evaluation of the relationship between renal function and the pharmacokinetic parameters
- Assessment of whether posology adjustment is warranted in patients with decreased renal function and development of dosing recommendations.

6.1. Parameter estimation

Plasma concentration data (and urinary excretion data if collected) should be analysed to estimate various parameters describing the pharmacokinetics of the drug and its active metabolites. The pharmacokinetic parameters include the area under the plasma concentration curve (AUC), peak concentration (C_{max}), and terminal half-life ($t_{1/2}$) for both parent compound and metabolites. For

parent compound also apparent clearance (CL/F) should be presented. For multiple-dose studies trough concentration (C_{min}) and fluctuation should also be presented. When appropriate (i.e. when the drug or metabolites exhibit a relatively high extent of plasma protein binding), parameters should be expressed in terms of unbound as well as total concentrations. In cases when urinary excretion data have been collected, renal clearance (CL_R) should be calculated. The choice of pivotal pharmacokinetic parameters to be used in dosage adjustment strategy should be justified by considering the available knowledge about the relationship between plasma concentrations or other pharmacokinetic parameters and efficacy or toxicity (see also 6.3).

6.2. Presentation of data and development of dosing recommendations

Presentation of data

Data should be presented in several ways:

- Graphical description of the relationship between renal elimination capacity and pharmacokinetics
- Modelling of the relationship between renal elimination capacity and pharmacokinetics
- Descriptive statistics (e.g. mean, SD, range, median) of the pharmacokinetic parameters according to renal function group (normal, mild, moderate, severely decreased renal elimination capacity and end stage renal disease)
- For a reduced-design study, the geometric mean ratios of the pharmacokinetic parameters in severe renal impairment versus control group should be presented with confidence intervals at the chosen significance level.

GFR should be expressed as the absolute value (ml/min). The graphical presentation should describe the relationship between individual pharmacokinetic parameters and renal elimination capacity (e.g. measure of GFR) as a continuous variable. This is important for the assessment of variability at normal and reduced renal function and facilitates the identification of cut-off GFR values for posology adjustment. The pharmacokinetic parameters of interest are usually CL/F, AUC, Cmax and, when appropriate, Cmin. If relevant, the pharmacokinetic parameters should be expressed in terms of unbound concentrations (see section 5.4).

Defining target exposure

For drugs where an effect of decreased renal function on drug exposure has been identified, the clinical relevance of the increased drug exposure or concentrations needs to be evaluated to determine if dose adjustment is needed. The aim is to develop dosing recommendations that will ensure that the patients will obtain treatment that is effective and safe. Factors that should be taken into account are the pharmacokinetic characteristics of the drug at decreased renal function and the PK/PD relationship regarding efficacy and safety, including a potentially altered PK/PD relationship in subjects with renal impairment.

Based on available information regarding PK/PD for efficacy and safety and/or the exposure at the therapeutic dose in the phase III population, a target exposure or target concentration range (whichever is more relevant for efficacy and safety) should be defined, within which no clinically relevant difference in efficacy and safety is expected. A thorough discussion of and justification for the chosen target as well as a description of how it was determined should be provided. The dosing recommendations should aim at allowing a majority of the patients to obtain exposure/concentrations within the defined target range.

The recommendations of posology adjustment should be based on comparison with subjects with renal function that is typical of the phase III patient population where efficacy and safety has been established, taking into account the major concern (side effects or lack of efficacy) for the specific product. In case the phase III patient population has decreased renal elimination capacity (e.g. elderly patients with GFR<90 ml/min) the need for a posology adjustment should be evaluated in patients with normal renal function as well as in patients with lower GFR than the phase III population. Depending on when the decreased renal function study is performed during the clinical development, the distribution of renal elimination capacity in the phase III clinical trial patient population may not be known at the time of conducting and evaluating the decreased renal function study. Although a preliminary dosage recommendation at decreased renal function can be made based on the data obtained in the decreased renal function study, the final evaluation and development of dosage recommendations at decreased renal function may need to await finalisation of the phase III studies.

Constructing the mathematical model

If a clinically relevant effect of decreased renal elimination capacity is observed, mathematical models should, if possible, be constructed to evaluate the relationship between measures of renal elimination capacity as a continuous variable and relevant pharmacokinetic parameters. The intended result is a model that can successfully predict the pharmacokinetic behaviour, given information about renal elimination capacity. Generally, this involves a regression approach in which measures of renal elimination capacity and the pharmacokinetic parameters are treated as continuous variables. One commonly used model is a linear relationship between GFR and CL/F of the drug. Other models (e.g. more mechanistic models) can be used if adequately supported by the data. Based on the estimated model, the predicted mean values of CL/F and AUC should be calculated and plotted against GFR in a graph with their associated confidence intervals as well as the prediction intervals. The method described above should also be used to describe exposure to major and/or active metabolites of the drug given renal elimination capacity.

For non-renally eliminated drugs, there might not be a linear relationship between GFR and drug clearance. When a staged design study has been performed, the decision how to analyse the results therefore needs to be made on a case-by-case basis. If the analysis is based on comparison of group means, the difference between group means should be presented with confidence intervals to aid interpretation of the data.

Developing dosing recommendations

Dosing recommendations should be based on absolute and not body-surface area-adjusted GFR. If there are active metabolites, the increase in total active moiety (sum of clinically relevant active entities, taking into account the potency and unbound exposure of each active entity) should guide the dosing recommendation. Based on the mathematical model, calculations can be made to identify doses and dosing intervals that will lead to exposure or concentrations within the target range in patients with decreased renal function. This may be achieved by a reduced dose, prolonged dose interval or a combination of both. The cut-offs for dose adjustments do not need to be the same cut-offs that were used for defining renal elimination capacity at recruitment to the study, but cut-offs for dose adjustments should be set to obtain optimal target attainment and reduction of the overall pharmacokinetic variability. With the aim to ensure that the major part of the patients will meet the selected target criteria, the dose could for example be adjusted to produce a comparable range of a pharmacokinetic parameter (e.g. AUC, C_{max}, or C_{min}) for the drug or active metabolites in both the typical patient and patients with decreased renal function.

In order to confirm the proposed dose recommendations, simulations of the steady state exposure at the recommended dose(s) should be provided. The simulations should preferably include graphical

description of (total and, when relevant, unbound) concentration over time, also showing the predicted variability in the population. Graphical description of relevant steady state pharmacokinetic parameters (e.g. AUC, C_{max}, or C_{min}) versus renal elimination capacity including appropriate measures for variability should also be supplied. It should be shown whether subjects with GFR just above and just below the cut-offs for dose adjustment obtain exposure within the target range. If estimates of pharmacokinetic variability in phase III are available, additional simulations using this information may be useful to assess the possible extremes of the distribution of the pharmacokinetic parameters. For an example of development of dosing recommendations for subjects with decreased renal function based on modelling and simulation of pharmacokinetic data, see Edholm *et al* 2008 (1).

For drugs with a narrow therapeutic index it should be considered whether specific dosing recommendations for decreased renal function are sufficient or whether also therapeutic monitoring of drug concentrations (TDM) or other types of monitoring should be recommended.

For patients with dialysis treatment, data should be used to determine a potential dose reduction as well as how/when the dose should be administered in relation to dialysis treatment. If possible, dosing recommendations should be developed also for not studied dialysis methods based on available data from one dialysis method, measures of dialysis adequacy (such as Kt/V, standardised Kt/V and Urea Reduction Ratio) and e.g. data from similar drugs. When no study has been performed in patients with dialysis treatment, the Applicant should discuss the potential for dialysis to influence the pharmacokinetics (taking into account potential differences between dialysis methods) and should include relevant information in the SmPC.

In the pharmacokinetic study, GFR should preferably be determined using an exogenous marker (e.g. iohexol), as discussed in section 5.2. However, it is recommended to present data and evaluate dosing recommendations also applying other methods such as estimation of GFR from serum creatinine (by e.g. the MDRD or CKD-EPI formulas) or from Cystatin C, or estimation of creatinine clearance (by e.g. the Cockcroft-Gault formula). Thereby it may be confirmed whether the dosage recommendations developed based on measured GFR (e.g. which GFR cut offs that should be used for dose adjustment) can be applied also using estimated GFR or estimated creatinine clearance. The cut-offs for dose adjustment should preferably be suitable regardless of which method for estimating renal function is used in clinical practice.

Other recommendations / warnings to consider

Consideration should be given to possible consequences of altered importance of other elimination pathways. For example, for a drug that is mainly eliminated by renal excretion and for which metabolism accounts for a minor part of the elimination, inhibition of the metabolic pathway or pharmacogenetic differences may not be an issue in patients with normal renal function. However, in severely decreased renal elimination capacity, the metabolic pathway becomes the major elimination route and e.g. inhibition by concomitant medication could result in large increases in exposure.

Consideration should also be given to the risk for an increase of inactive metabolites to potentially toxic levels, as this cannot be handled by dose reductions. Recommendations must then be developed on a case-by-case basis.

For drugs that are likely to be administered to patients with acute kidney injury/disease/failure and rapidly changing renal function, e.g. patients in intensive care units, dosing might need to be based on plasma concentration measurements or efficacy markers. For such drugs it is therefore recommended to develop clinically feasible methods for drug monitoring.

Extrapolation to elderly and paediatric patients

Results from renally impaired, otherwise healthy, adult volunteers can likely be extrapolated to elderly patients with similar absolute GFR. The relative effect of an altered GFR on the pharmacokinetics of a drug, as compared with normal GFR for the patient population, may in most cases also be extrapolated from adults to the paediatric population. However, due to ongoing maturation of the kidney in the very young children, special consideration should be given to drugs that are metabolised or renally transported to a major extent (see also Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population [CHMP/EWP/14701372004] and Guideline on the investigation of medicinal products in the term and preterm neonate [EMEA/536810/2008]).

7. Labelling issues

The information in the SmPC should follow the guidance on the Summary of Product Characteristics in the Notice to Applicant, Volume 2C.

Specific dosing recommendations should be given in section 4.2 with cross-reference to section 5.2, and, when relevant, to sections 4.3 and/or 4.4. Also when no posology adjustment is needed, this should be stated in section 4.2. Preferably, renal elimination capacity should be expressed as GFR (ml/min), but if creatinine clearance (measured or estimated) has been used to estimate renal elimination capacity in the pharmacokinetic study, this should be made clear in section 4.2. Information on which methods for estimating GFR (or creatinine clearance) that have been shown to be appropriate to use for dose adjustments should be provided in section 4.2. If dose recommendations (e.g. which cut off GFR values should be used for dose adjustment) may differ to a clinically relevant extent depending on which method is used for measuring or estimating GFR, this should be described.

Lack of information regarding influence of decreased renal function on the pharmacokinetics could result in a contraindication (section 4.3) or warning (section 4.4) regarding e.g. several renal impairment, depending on the characteristics of the drug. Lack of data should generally not lead to a contra-indication unless there is a specific safety concern. For drugs with a narrow therapeutic index the possibility of therapeutic drug monitoring or monitoring of exposure based on clinical markers for efficacy and/or safety may be considered.

Information regarding the influence of decreased renal function on the pharmacokinetics should be given in the *Special populations* sub-section of section 5.2. The information should include effects on parent compound and metabolites and when relevant include effects on protein binding and unbound exposure. Information on which method was used to measure (or estimate) GFR in the study in decreased renal function should also be provided. When pharmacokinetics in patients with decreased renal function has not been evaluated, this should be mentioned in section 5.2. This section could include information that decreased renal function is unlikely to affect the pharmacokinetics to a clinically relevant extent, if this has been well justified.

In case a clear relationship is found between renal function and one of the relevant pharmacokinetic variables, the formula can be included in section 5.2.

The Elimination sub-section of section 5.2 should include information regarding extent of renal elimination of parent compound and metabolites and mechanism of renal elimination (e.g. extent of filtration and active secretion). Available information on which transporters are involved in the active secretion should also be provided.

In case the drug has been shown to be removed by dialysis treatment, this information may be given in section 4.9 (Overdose).

Definitions

GFR	glomerular filtration rate
absolute GFR	GFR in ml/min
renal elimination capacity	is in this guideline defined as GFR in ml/min, and may not necessarily be directly related to renal disease
renal impairment	is in this guideline generally used to indicate renal disease
renal function	is in this guideline used as a comprehensive term. 'Decreased renal function' may indicate physiologically decreased renal elimination capacity as well as renal disease

References

1. Edholm M *et al*: Regulatory aspects of pharmacokinetic profiling in special populations. Clin Pharmacokinet 2008:47(11), 693-701