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/225702).

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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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 may need to 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 efficacy/safety study population. The need to perform a pharmacokinetic study in subjects with decreased renal function and the design and conduct of such a study depends 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.

The current revision includes clarifications in most sections of the guideline, e.g. on the advice to study the effect of reduced renal function on drugs that are primarily hepatically eliminated and the recommendation to use an accurate method for determination of glomerular filtration rate (GFR) in the subjects included in the pharmacokinetic study. In addition, the recommendation to use an absolute measure of renal function (in ml/min) in the dosing recommendations for patients with impaired renal function has been emphasised.

1. Introduction (background)

Renal function can be decreased either through renal disease/renal toxicity 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, and in plasma protein binding , especially in patients with severely impaired renal function. Effects of severe renal impairment on non-renal elimination mechanisms have been suggested to be attributed to accumulation of uremic toxins that inhibit or suppress metabolising enzymes and transport proteins. Renal impairment may also alter the exposure-response relationship (pharmacodynamics, efficacy, safety) for a drug.

Pharmacokinetic data can be used to extrapolate efficacy and safety data from the population included in phase III or other pivotal efficacy/safety studies to subpopulations that were not sufficiently represented in the pivotal studies. Thus, a pharmacokinetic study can be performed to estimate drug exposure in patients with decreased renal function, and alternative dosing regimens may be developed based on the degree of change in drug exposure and the relationship between exposure and efficacy and exposure and safety.

Renal function is usually assessed based on glomerular filtration rate (GFR). 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. In this guideline, measured GFR is defined as a GFR determined by using an exogenous substance, while estimated GFR is defined as a GFR estimated from an endogenous marker. The gold standard for assessment of renal function is a measured GFR using an exogenous substance as a filtration marker (e.g. inulin, ^{51}Cr-EDTA, ^{99m}Tc-DTPA, iothalamate, iohexol). Methods for estimating GFR using endogenous markers have different drawbacks and are not considered as accurate as measured GFR. Renal function can also be assessed based on creatinine clearance, which can be measured by urinary excretion of creatinine or estimated from creatinine concentrations in plasma. However, as creatinine is not only filtered but also secreted, creatinine clearance may overestimate GFR.

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For diagnosis, prognosis and treatment of renal disease, the degree of renal impairment is generally categorised based on body size-normalised glomerular filtration rate (GFR) in ml/min/1.73 m^2. However, renal elimination capacity is correlated to absolute GFR, in this guideline defined as GFR in ml/min. Therefore dose recommendations for a renally eliminated drug should be based on absolute GFR (or other measure for renal function in ml/min), and not on GFR normalised to a body surface area of 1.73 m^2.

In this guideline, the term drug generally refers to a pharmacologically active parent compound but, although not mentioned in every subsection of the document, the effect of renal impairment on the exposure to clinically relevant active metabolites should always be considered. Clinically relevant active metabolites, or major 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.

2. Scope

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

- Situations in which pharmacokinetic studies 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 the clinical investigation of the pharmacokinetics of therapeutic proteins [CHMP/EWP/89249/2004]

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/147013/2004]

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 subjects with decreased renal function

If there is a risk of clinically relevant increases in exposure to a drug or active metabolite in patients with renal impairment, a pharmacokinetic study in subjects with decreased renal function may be necessary in order to obtain adequate treatment recommendations.

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The risk of a clinically relevant increase in exposure in renal impairment is expected to be largest for drugs that are primarily renally eliminated. For such drugs a pharmacokinetic study in subjects with decreased renal function should be conducted, unless otherwise justified. A pharmacokinetic study in subjects with decreased renal function is recommended also for primarily hepatically eliminated drugs, as a risk of increased exposure due to renal impairment cannot be completely excluded for these drugs (see section 1). Examples of drugs for which it may be justified not to perform a pharmacokinetic study in subjects with decreased renal function include:

- drugs intended for single or occasional administration and for which a prolonged elimination of the drug/active metabolite is not a safety problem

- drugs/major active metabolites that are eliminated primarily via non-renal and non-hepatic routes

- large proteins that are not expected to undergo glomerular filtration (see Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins [CHMP/EWP/89249/2004]). However, specific consideration may need to be made for an antibody-drug conjugate (ADC) or other large protein conjugated to a small molecule drug

- drugs without relevant systemic absorption

- drugs that are predominantly hepatically eliminated and for which safety data are available indicating that dose adjustments are not necessary even at a markedly increased exposure to the drug (see also 6.2)

- drugs that are predominantly hepatically eliminated and for which a potential increase in exposure due to renal impairment can be handled in clinical practice, e.g. by individual dose titration based on monitoring of relevant markers for efficacy and/or tolerability

- drugs not indicated for use in patients with renal impairment (e.g. due to foreseen safety issues or lack of effect in a renally impaired population)

- drugs that cannot be administered to otherwise healthy subjects for safety reasons and a study in patients (i.e. with the condition which the drug is intended for) is not feasible or justifiable

If no study is performed in subjects with decreased renal function, a justification should be given (e.g. in the Summary of Clinical Pharmacology in Module 2 of the Marketing Authorisation Application). In such cases, the Applicant should discuss the risk of effects of decreased renal function on the pharmacokinetics of parent drug, clinically relevant active metabolites and, if relevant, inactive metabolites (see section 5.4) and should include relevant information in the SmPC (see section 7). Lack of data may lead to restriction in the use.

Effect of dialysis

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 or a clinically relevant active metabolite, evaluation of the influence of dialysis treatment on the pharmacokinetics is recommended (see section 5.5).

Timing of study

If the target population for the drug is expected to include a relatively large proportion of patients with renal impairment, and if a specific treatment recommendation is likely to be needed in these patients, it may be valuable to obtain efficacy and safety data from patients with renal impairment in the pivotal efficacy/safety study(ies). This may be particularly important if an altered exposure-response or

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exposure-safety relationship is expected in renal impairment. In such cases, conduct of a pharmacokinetic study in subjects with decreased renal function before initiating the pivotal efficacy/safety trial should be considered. If information on the influence of decreased renal function on the pharmacokinetics of the drug is available when the clinical development programme is designed, it may be possible to give appropriate dosage recommendations in patients with renal impairment and restrictions in the inclusion/exclusion criteria concerning renal function in the pivotal study may be avoided.

5. Study design

The primary goal of a pharmacokinetic study in 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 specific treatment recommendations are needed in this population.

A pharmacokinetic study in subjects with decreased renal function may have a "full-range design" or be a reduced or staged study (see section 5.1). If renal impairment is expected to lead to clinically relevant increases in exposure to the drug and/or active metabolite, i.e. if a need for dose adjustments in patients with different degrees of renal impairment is anticipated, a study with a "full-range study design" is recommended.

Otherwise, 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 severely decreased renal function (see section 5.1) does not alter the pharmacokinetics of the drug or active metabolite to a clinically relevant extent, no further study is warranted. If, based on the effect of severely decreased renal function on drug exposure (or another relevant pharmacokinetic parameter, see section 6.2), a risk of a clinically relevant difference in pharmacokinetics at other degrees of renal impairment cannot be excluded, then 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* the 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 preferably 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 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 justified.

5.1. Study population

The pharmacokinetic study may be conducted in otherwise healthy volunteers or in patients with the condition for which the drug is intended, depending on e.g. the safety profile of the drug to be studied. In either case, a wide range of renal function enhances the ability to detect and characterise the effect of renal function on the pharmacokinetics.

Renal function groups are in this guideline defined based on *absolute* GFR (ml/min) as outlined in Table 1, i.e. an absolute GFR< 90 ml/min is defined as decreased renal function regardless of e.g. the age or body size of the subjects. The term 'control group' is used for the group best representing renal function in the studied or proposed pivotal efficacy/safety study population and may, thus, not necessarily be the group with normal renal function as defined in Table 1.

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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.

Table 1. Renal function groups

Group	Description	GFR (ml/min)
1	Normal renal function	≥ 90
2	Mildly decreased renal function	60- <90
3	Moderately decreased renal function	30- <60
4	Severely decreased renal function	<30 not requiring dialysis
5	End stage renal disease (ESRD)	<15 requiring dialysis treatment

A full-range study should, if feasible, include subjects covering the full renal function range (Table 1) including ESRD subjects (see sections 5.3 and 5.5). 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. However, in order to determine the relationship between GFR and drug clearance, it is more important to obtain an adequate representation over the whole range of GFR than to have equal numbers per group. It is particularly important to aim for representation at the lower GFR values in the group with severely decreased renal function (≤20 ml/min).

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 toxins. 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 (preferably not higher than 20 ml/min) but not requiring dialysis treatment, as they would be expected to have accumulation of uremic toxins. 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, the study should be expanded (staged study). The decision on which renal function groups to add should be based on which other degrees of decreased renal function could be expected to affect the pharmacokinetics of the study drug, based on the effect in the group with severely decreased renal function. 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.

5.2. Measures of renal function

In order to have a reference measure of renal function that is independent of clinical practice at the time of conduct of the pharmacokinetic study, it is recommended that a method accurately measuring GFR using an exogenous marker is used to determine renal function in the subjects in the pharmacokinetic study, if possible. This may be particularly important for drugs that are expected to be affected by renal impairment to such an extent that dose adjustments will be needed and where it, e.g. due to a relatively narrow therapeutic index, is critical that dose adjustments are made at a certain GFR cut-off. In other cases, e.g. in a reduced-design study of a hepatically eliminated drug or if the dose can be individually titrated based on clinical monitoring, it may be less critical to have an

accurate measure of GFR in the pharmacokinetic study, and the use of estimation methods may be sufficient.

As discussed in the Introduction, renal elimination capacity is related to absolute GFR. When presenting the results of the pharmacokinetic study and developing dose recommendations (see section 6.2), GFR should therefore be expressed as ml/min. If a formula providing BSA-normalised GFR (ml/min/1.73 m^2) has been used to estimate renal function in study subjects, this should be recalculated to the absolute GFR in ml/min in each individual.

If assessment of renal function is based on creatinine concentration in plasma, creatinine should be measured with a method, preferably an enzymatic method, with results that are traceable to a reference measurement procedure.

5.3. Drug administration

If the drug and its active metabolites are expected to exhibit dose-linear and time-independent pharmacokinetics in renally impaired individuals, 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 be administered to all subjects in the study, regardless of renal function, unless a potential increase in single-dose exposure is a safety concern.

If steady state pharmacokinetics of the drug or an active metabolite cannot be predicted from single-dose data due to dose- or time-dependent pharmacokinetics, a multiple-dose study is desirable. The doses in a multiple-dose study should be chosen aiming at achieving drug concentrations that are within the clinical therapeutic concentrations range. 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 function. 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.

In ESRD subjects included in a full-range study, the drug should be administered between dialysis sessions (on a non-dialysis day) in order to establish how the residual GFR affects drug clearance. If evaluation of the effect of dialysis treatment on drug clearance (dialysis clearance) is also indicated, drug exposure at administration on a dialysis day (just before dialysis) should be compared with administration on a non-dialysis day (see section 5.5).

5.4. Sample collection and analysis

Plasma (or whole blood, as appropriate, and optionally urine) samples should be analysed for parent drug and major metabolites with known or suspected activity (therapeutic or adverse). If the parent drug is an inactive prodrug that is rapidly and completely converted to one or more active metabolites, the inactive parent drug does generally not need to be analysed. Metabolites that are excreted by the renal route will accumulate in patients with renal impairment. 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 renal impairment 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 high extent of plasma protein binding (>90%) 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*, pre-dose plasma samples from the subjects included in the pharmacokinetic study (all groups) spiked with radiolabelled drug may be used. The spiked concentrations should be chosen taking into account potential concentration dependency in protein binding.

5.5. Dialysis

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.

The primary question to be addressed in a study of dialysis treatment on the pharmacokinetics of a drug is whether the dose regimen should be adjusted as a consequence of dialysis treatment. The results of a dialysis study also provide insight regarding the value of dialysis for treatment of overdose. Assessment of the effect of dialysis treatment may be integrated with the study of the effect of decreased renal function.

To study the effect of dialysis, 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 may be collected in order to determine the amount of study drug extracted during dialysis treatment.

The dialysis methods expected to be used in the intended patient population should preferably be studied. Intermittent haemodialysis is usually the most important method to be evaluated, as it is the most commonly used in ESRD patients. Extrapolation of the effect of intermittent haemodialysis on the pharmacokinetics of drugs to other modes of dialysis is difficult and can be misleading. Therefore, if a clinically relevant effect on the pharmacokinetics of the drug is observed in haemodialysis patients, pharmacokinetic studies should also be considered in subjects 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.

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If a drug is not expected to be largely affected by dialysis (e.g. due to high protein binding, a large volume of distribution or a high non-renal clearance), a study to evaluate the effect of dialysis treatment on drug clearance is not necessary.

5.6. Population pharmacokinetic analysis of sparse data

Evaluation across a wide range of renal function enhances the ability to detect and characterise the effect of renal function on the pharmacokinetics of a drug. Patients with severe renal impairment or ESRD are often excluded from clinical efficacy and safety studies (or are included only in very low numbers) and consequently seldom included in population pharmacokinetic analyses of data from phase II/III studies. Hence, if evaluation of effects of renal function on an investigational drug is indicated (see section 4), it is recommended to conduct a full-range or reduced design phase I study (see section 5.1). This is considered especially important for renally eliminated drugs where exposure is expected to be increased in patients with renal impairment and a need for dose adjustment is anticipated.

If a population pharmacokinetic analysis is used to evaluate the effect of renal function on pharmacokinetics of a drug, the analysis should be pre-planned. The analysis should include a sufficient number of patients and a representative range of renal function so that the study can describe relevant pharmacokinetic differences. Simulation-based evaluation of the study design (stochastic simulation and estimation) to determine the power to detect a clinically relevant effect of decreased renal function is recommended. In cases where concentrations of potentially active/toxic metabolites and/or unbound concentrations are of importance, these would need to be analysed. Renal function should be estimated repeatedly during the study and as close in time as possible to the pharmacokinetic sampling time-points. Renal function could then be handled as a time-varying factor in the analysis.

The population pharmacokinetic analysis should be performed according to best practices. The model should be qualified in relation to its purpose. The predictive properties for the different degrees of renal function should be demonstrated and the precision in the estimated effect should be evaluated using adequate methods. 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 model-estimated effect of decreased renal function (95% confidence intervals) should be determined using methods not assuming symmetrical distribution, e.g. bootstrapping or log-likelihood profiling.

Results of the population analysis should not be extrapolated outside the studied range. Of note, the lower end of the renal function in the anticipated target patient population must be adequately represented in order to ascertain that the effects in this group are captured.

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 function on drug elimination is limited and recommendations for the use of PBPK cannot be given in this guideline. However, the field of PBPK is evolving and it is foreseen that before the next revision of the guideline, PBPK modelling may become useful for predicting effects of decreased renal elimination capacity on drug disposition.

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5.8. Pharmacodynamic assessments

Pharmacodynamics may be altered in renal impairment, which could lead to an altered exposure-response relationship. If that is the case, information regarding the exposure-response 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, if relevant, 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 important when the mechanism of action is known to be related to renal function.

6. Data analysis

The primary intent of the analysis of data from a pharmacokinetic study in subjects with decreased renal function is to assess whether posology adjustment is required for renally impaired patients, and, if so, to develop dosing recommendations based on measures of renal function. The final data analysis of all available data in subjects/patients with decreased renal function may need to be performed at a late stage of drug development as it should preferably take into account exposure-response data from pivotal efficacy/safety studies (see below). The data analysis and other background for the proposed recommendations for patients with renal impairment may therefore be presented e.g. in the Clinical Overview and/or Summary of Clinical Pharmacology in Module 2 of the Marketing Authorisation Application, and/or in a separate report.

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 studied 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 apparent clearance (CL/F) should also be presented. For multiple-dose studies trough concentration (C_{min}) and fluctuation should also be presented. When appropriate (i.e. when the drug or active metabolites exhibit a high extent of plasma protein binding, see 5.4), 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 a dosage adjustment strategy should be justified by considering the available knowledge about the relationship between plasma concentrations or other pharmacokinetic parameters and efficacy and toxicity (see section 6.2).

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6.2. Presentation of data and development of dosing recommendations

6.2.1 Presentation of data

Data should be presented in several ways:

- Graphical description of the relationship between renal function measure 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 function and end stage renal disease) and geometric mean ratios versus control group

- For a reduced-design study, the geometric mean ratios of the pharmacokinetic parameters in the group with severely decreased renal function (see section 5.1) versus control group should be presented with confidence intervals at the chosen significance level.

The renal function measure should be expressed as the absolute value (ml/min).

The graphical presentation should describe the relationship between individual pharmacokinetic parameters and a measure of renal function as a continuous variable. This is important for the assessment of variability at normal and reduced renal function and facilitates the identification of the degree of renal impairment at which the dose should be adjusted. The pharmacokinetic parameters of interest are usually CL/F, AUC, C_{max} and, when appropriate, C_{min}. If relevant, the pharmacokinetic parameters should be expressed in terms of unbound concentrations (see section 5.4).

6.2.2 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 exposure-response relationship regarding efficacy and safety, including a potentially altered exposure-response relationship in patients with renal impairment.

Based on available information regarding the exposure-response relationship for efficacy and safety and/or the exposure at the therapeutic dose in the pivotal efficacy/safety trial 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 pivotal efficacy/safety trial 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. Depending on when the decreased renal function study is performed during the clinical development, the distribution of renal function in the pivotal efficacy/safety trial patient population may not be known at the time of conducting and analysing the decreased renal function study. Although a preliminary dosage recommendation for 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 for decreased renal function may need to await finalisation of the pivotal efficacy/safety studies.

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6.2.3   Constructing the mathematical model

If a clinically relevant effect of decreased renal function is observed, mathematical models should, if possible, be constructed to evaluate the relationship between measures of renal function as continuous variables and relevant pharmacokinetic parameters. The intended result is a model that can successfully predict the pharmacokinetic behaviour, given information about renal function. Generally, this may involve a regression approach in which measures of renal function and the pharmacokinetic parameters are treated as continuous variables. The modelled function can be illustrated in a graph together with individual CL/F and/or AUC data plotted against a renal function measure as a continuous variable. The method described above should also be used to describe exposure to major and/or active metabolites of the drug given renal function.

6.2.4   Developing dosing recommendations

Dosing recommendations should be based on absolute GFR (or other measure of renal function) in ml/min and not GFR normalised to a body-surface area of 1.73 m^2. 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 to 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 renal impairment. This may be achieved by a reduced dose, prolonged dose interval or a combination of both. The cut-offs for dose adjustments should be set to ensure that the majority of patients, regardless of GFR, will reach optimal (target) exposure, and should not by default be the same cut-offs as those used for defining renal function groups at recruitment to the study, i.e. the cut-offs can be set at other GFR values than 30, 60 and 90 ml/min.

In order to confirm proposed dose recommendations, it is recommended to perform simulations of the steady state exposure at the recommended dose(s). The simulations should be presented as a graphical description of relevant steady state pharmacokinetic parameters (e.g. total or unbound AUC, C_{max}, or C_{min}) versus renal function as a continuous variable, including appropriate measures for variability. It should be shown whether subjects with renal function just above and just below the cut-offs for dose adjustment obtain exposure within the target range. If estimates of pharmacokinetic variability in the pivotal efficacy/safety trials are available, additional simulations using this information may be useful to assess the possible extremes of the distribution of the pharmacokinetic parameters at a given GFR. If a change in dose interval is proposed, the simulations should preferably include graphical description of concentration over time.

For drugs with a narrow therapeutic index it should be considered whether specific dosing recommendations for renal impairment are sufficient or whether also therapeutic monitoring of drug concentrations (TDM) or other types of monitoring should be recommended. In case of TDM, it needs to be considered whether plasma protein binding might be altered in renal impairment and, thus, whether TDM can be based on total concentrations.

For patients with dialysis treatment, data should be used to determine a potential dose adjustment as well as how/when the dose should be administered in relation to dialysis treatment. When no study has been performed in patients with dialysis treatment, the Applicant should discuss the potential for dialysis to influence the pharmacokinetics and should include relevant information in the SmPC.

6.2.5   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

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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 severe renal impairment, 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 of 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.

For fixed-combination products, including one or more substances for which dose adjustment is necessary at renal impairment, it needs to be considered whether the product is useful in patients with renal impairment or if monocomponent products should be recommended instead.

6.2.6 *Extrapolation to elderly and paediatric patients*

The relative effect of an altered GFR on the pharmacokinetics of a drug, as compared with normal GFR in the target patient population, may in most cases be extrapolated from adults to an elderly or a paediatric population. However, for very young children who might have ongoing maturation of the kidney 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 function should be expressed as GFR (ml/min), but if creatinine clearance (measured or estimated) has been used to estimate renal function in the pharmacokinetic study, this should be made clear in section 4.2. If dose adjustment at a certain GFR is critical for adequate safety and/or efficacy, it may need to be clarified in section 4.2 that for dose adjustment, the individual patient's renal function should be estimated by absolute GFR in ml/min.

Depending on the characteristics of the drug, a 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) below a certain degree of renal function. Lack of data alone 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 pharmacokinetics should be given in the *Special populations* sub-section of section 5.2. The information should include effects on exposure and, if relevant, half-life of parent compound and relevant metabolites. When relevant, effects on

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unbound exposure should be described. If available, information of the effect of dialysis treatment on the drug should also be included, e.g. describing the proportion of the drug removed by dialysis.

Information on which method was used to measure (or estimate) renal function in the study in decreased renal function should be provided in section 5.2. If renal function was estimated based on creatinine concentration in plasma, it should be mentioned which analysis method was used for determining creatinine.

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).

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