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**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

**NOTE FOR GUIDANCE ON THE EVALUATION OF THE
PHARMACOKINETICS OF MEDICINAL PRODUCTS IN PATIENTS
WITH IMPAIRED RENAL FUNCTION**

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Note:

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

- Pharmacokinetic Studies in Man (Notice to Applicant, Vol. 3C C3A, 1987)
- The Investigation of Drug Interactions (CPMP/EWP/560/95)
- Investigation of Chiral Active Substances (Notice to Applicant, Vol. 3C C29a, 1994)
- Modified Release Oral and Transdermal Dosage Forms: Section II (Pharmacokinetic and Clinical Evaluation) (CPMP/EWP/280/95)
- The Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98)
- Validation of Analytical Procedures (ICH topic Q2A and Q2B)
- Structure and Content of Clinical Study Reports (ICH topic E3)
- Good Clinical Practice (ICH topic E6)
- General Considerations for Clinical Trials (ICH topic E8)

This Note is intended to assist applicants during development of medicinal products. It is only a guidance; any deviations from the guidelines should be explained and discussed in the Clinical Overview.

I. INTRODUCTION

Pharmacokinetic studies are used as a tool to identify a sub-population, such as patients with renal impairment, for which an alternative dosing regimen is indicated for efficacy or safety reasons. Renal function can be decreased either through renal disease or as a consequence of ageing with the decline starting during the fourth decade. Renal impairment has not only been associated with diminished drug and metabolite excretion but also with changes in absorption, renal and hepatic metabolism, plasma protein binding and distribution, especially in patients with severely impaired renal function. In addition, pharmacodynamics may also be altered in renal impairment.

Factors that influence the need to conduct a pharmacokinetic study in renal impairment are the intended use of the drug, pharmacokinetic characteristics of the drug and PK/PD relationships regarding efficacy and safety. It is important to identify the major concern (side effects or lack of efficacy), given the intended therapeutic use of the drug. For example, for a specific drug, it may be more important to maintain plasma concentrations above a certain minimum concentration in all patients than to avoid excessive plasma concentrations in some patients.

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

- In what situations studies of pharmacokinetics should be performed in subjects with impaired renal function and in patients on dialysis
- The design and conduct of pharmacokinetic studies in subjects with impaired renal function
- Data analysis, presentation and evaluation of results of such studies
- Reflection of these results in the SPC.

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

A pharmacokinetic study in patients with impaired renal function is recommended when renal impairment is likely to significantly alter the pharmacokinetics of the drug and/or its active metabolites and a posology adjustment may be needed for such patients taking into account the PK/PD relationship.

Pharmacokinetic characterisation in patients with severe renal impairment should be considered even if the drug and/or its active metabolite(s) are eliminated mainly by metabolism, as severe renal impairment may affect the pharmacokinetics of the drug through diverse mechanisms. This is especially applicable if the drug has a narrow therapeutic index.

Evaluation of the influence of dialysis on the pharmacokinetics should also be considered. This is further discussed in section II.8 below.

If no study is performed in patients with renal impairment, a justification should be given. In such case, the applicant should discuss the potential for renal impairment to influence the pharmacokinetics (of parent drug, active and “inactive” metabolites) and should include relevant information in the SPC (see also section IV). Lack of data may lead to restriction in the use (warnings or contraindications).

When a posology adjustment is likely to be needed in patients with impaired renal function, 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 renal impairment 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 reduced renal function.

III. STUDY DESIGN

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

III.1 Study 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 degree of renal function. In either case, a wide range of degrees of renal impairment enhances the ability to detect and characterise the effect of renal function on the pharmacokinetics. In case a reduced study design (see section II.5) is not used, the study should, if feasible, include subjects covering the full range from severely impaired to normal renal function. To ensure adequate representation, approximately equal numbers of subjects from each of the renal function groups (Table 1) should be recruited. If reliable information regarding pharmacokinetics in mild (or mild and moderate) renal impairment is available e.g. from phase III population pharmacokinetic analysis, this renal function group does not need to be included in the pharmacokinetic study (see also section II.6). The renal function groups should be comparable with respect to factors, which are expected to significantly influence the pharmacokinetics of the drug. Depending on the characteristics of the specific drug, these may be demographic factors such as age, gender or weight or other factors.

Table 1. Renal function groups

Group	Description	GFR (ml/min/1.73 m ²)
1	Normal renal function	> 80
2	Mild renal impairment	50-80
3	Moderate renal impairment	30-<50
4	Severe renal impairment	<30
5	End stage renal disease (ESRD)	Requiring dialysis

Use of a within study control group is recommended. Use of a pre-specified historical subject population of adequate size (including studies that may be initiated following the conduct of the renal insufficiency study), and model for confounding variables such as age, gender, weight and race using e.g. an ANCOVA model could be an alternative to a within-study control group. However, this requires that there are no study specific factors influencing the results, e.g. bioanalytical method or study conditions.

The number of subjects enrolled should be sufficient to detect clinically relevant pharmacokinetic differences. The “clinically relevant” difference should be pre-specified and justified on the basis of well documented concentration-response relationship of the parent drug and/or its metabolites (see also section III).

III.2 Measures of Renal Function

Renal function is usually assessed by measuring glomerular filtration rate (GFR). A number of exogenous markers for measuring GFR (e.g. 51Cr-EDTA, 99mTc-DTPA, iothalamate, iohexol) and endogenous markers for estimation of GFR (e.g. creatinine, Cystacin C) are available. It is recommended that renal function in pharmacokinetic studies is determined by measuring GFR using accurate well established methods (such as iohexol clearance).

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 renal impairment on the pharmacokinetics. Such methods are encouraged as useful additions in renal impairment studies.

III.3 Drug Administration

A single-dose study is sufficient when the drug and its active metabolites exhibit linear and time-independent pharmacokinetics. A multiple-dose study is desirable when the drug or an active metabolite is known to exhibit non-linear or time-dependent pharmacokinetics.

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. 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 renal impairment.

III.4 Sample Collection and Analysis

Plasma (or whole blood, as appropriate, and optionally urine) samples should be analysed for parent drug and any metabolites with known or suspected activity (therapeutic or adverse). Metabolites that are excreted by the renal route will accumulate in patients with renal impairment. Also, 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 such metabolites should be considered. 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, the pharmacokinetics should be described and analysed with respect to the unbound concentrations of the drug and active metabolites in addition to total concentration. 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 timepoints post-dose and use this unbound fraction in calculation of unbound exposure. An alternative could be an assessment of the effect of pre-dialysis plasma (plasma taken from a dialysis patient shortly before dialysis) on plasma protein binding in vitro. If no change in protein binding is observed in pre-dialysis plasma, evaluation of unbound exposure in the pharmacokinetic study is not needed.

III.5 Reduced/staged study design

A reduced or staged study design may be applicable e.g. if the applicant wants to confirm that the pharmacokinetics is not altered to a clinically relevant extent. In a reduced design only subjects at the extremes of renal function (i.e., subjects with normal and severely impaired renal function) are included. If the results confirm that renal impairment does not alter the pharmacokinetics to a clinically relevant extent, no further study is warranted. If the results do not support such a conclusion, the intermediate renal function groups (mild and moderate renal impairment) should also be studied (staged study). In this case, the results from all groups should be combined in the subsequent data analysis. In the reduced study design, subjects from the normal and severe renal function groups should preferably be matched regarding factors which are expected to significantly influence the pharmacokinetics of the drug, such as age, gender and weight. In the staged study design, the mild and moderate renal function groups should be comparable with the normal and severe groups with respect to these characteristics.

III.6 Population pharmacokinetics

A population pharmacokinetic evaluation of patients participating in phase II/phase III clinical trials can be used to assess the impact of renal function on the pharmacokinetics of a drug. This type of evaluation is valuable as it involves assessment of the effect of renal impairment on the pharmacokinetics in the target population.

In case a pharmacokinetic study in patients with renal impairment has been conducted prior to phase III, a subsequent population analysis can be used to confirm the results of the specific renal impairment study.

In other cases, a population pharmacokinetic study design and analysis can, in principle, be an acceptable alternative to a specific renal impairment study if it is pre-planned and includes a sufficient number of patients and a representative range of renal function so that the study could detect relevant pharmacokinetic differences. 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 in the population studies, if the population analysis is going to be used as an alternative to a specific renal impairment study. As data are observational, consideration should be given to possible imbalances in e.g. age, gender or weight between patients with different degrees of renal function. Obtaining a measurement of GFR may not be feasible in these patients. An acceptable, although less accurate, alternative for determining renal function in population analyses is estimation of GFR e.g. by calculation of creatinine clearance from serum creatinine and demographic data, as mainly patients with mild and moderate renal impairment are expected to be included in these studies.

Patients with severe renal impairment are often excluded or poorly represented in population pharmacokinetic studies. When this is the case, a separate and complementary study could be conducted to assess the pharmacokinetics in subjects with severe renal impairment (e.g., a study evaluating the pharmacokinetics in subjects with severely impaired renal function compared with subjects with renal function typical for the phase III population). The data from both sources should be used in the overall assessment of the effect of renal impairment. If different methods for measurement of renal function have been used in the population analysis and in the renal impairment study, this must be taken into account during evaluation of the results, especially if the methods do not give completely comparable estimations of GFR.

III.7 Pharmacodynamic assessments

The usability of dose-response data from phase II/III may be limited, e.g. due to study design issues, when it comes to interpreting the clinical relevance of observed pharmacokinetic changes. Hence, knowledge about the PK/PD relationships for efficacy and safety is important for the development of appropriate dosing recommendations. 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 or safety is included within the specific pharmacokinetic study in patients with renal impairment. This is especially relevant when the mechanism of action is known to be related to the renal function.

III.8 Dialysis

Dialysis may significantly alter the pharmacokinetics of drugs. When a significant fraction of the drug or active metabolite(s) is removed by dialysis, a change in the dosing regimen may be required, such as a supplementary dose following the dialysis procedure. It should be remembered that also drugs that are not excreted by the renal route to a large extent may be removed by dialysis.

For drugs that are likely to be administered to end-stage renal disease (ESRD) patients undergoing dialysis and where the drug or active metabolites are likely to be extracted during dialysis to such an extent that supplementary dosing after dialysis may be required, evaluation of the pharmacokinetics under both dialysis and nondialysis conditions should be considered in order to determine the contribution of dialysis to the elimination of the drug and potentially active metabolites. Primary questions to be addressed are whether the dosage regimen should be adjusted as a consequence of dialysis. The results of the study also provide valuable insight regarding the value of dialysis for treatment of overdose. The assessment of pharmacokinetics in dialysis may be integrated with the pharmacokinetics in the renal impairment study, as described above, or it may be conducted as a separate study. Intermittent haemodialysis is usually the most important method to be evaluated, as it is the most commonly used in ESRD patients.

Pharmacokinetic studies should also be considered in other dialysis situations such as continuous ambulatory peritoneal dialysis if the drug is likely to be used in such patients and these dialysis methods are likely to significantly affect the pharmacokinetics.

Seriously ill patients with acute renal failure are often treated with continuous haemofiltration/haemodialysis. It may be difficult to directly extrapolate the effect of intermittent haemodialysis on the pharmacokinetics of drugs to continuous haemodialysis or haemofiltration. However, based on available data (e.g. in intermittent haemodialysis, data

from similar drugs, in vitro data) the applicant should attempt to provide appropriate dosing recommendations also in these patients.

When no studies have been performed in dialysis patients, 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 SPC (see also section IV). When information regarding influence of one dialysis method is available, it should be discussed to what extent these data could be extrapolated to other dialysis situations.

IV. DATA ANALYSIS

The primary intent of the data analysis is to assess whether posology adjustment is required for patients with impaired 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 impaired renal function and development of dosing recommendations

IV.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}), 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 (CLR) 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 concentration-effect and concentration-toxicity relationship (see also III.3).

IV.2 Presentation of data

Data should be presented in several ways:

- Graphical description of the relationship between renal function and pharmacokinetics
- Modelling of the relationship between renal function and pharmacokinetics
- Descriptive statistics (e.g. mean, SD, range, median) of the pharmacokinetic parameters according to renal function group (normal, mild, moderate, severe renal impairment and end stage renal function)

The graphical presentation should describe the relationship between individual pharmacokinetic parameters and renal function (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 levels for posology adjustment. The pharmacokinetic parameters of interest are usually CL/F, AUC, C_{max} and C_{min}, when appropriate, expressed in terms of unbound concentrations.

Mathematical models may be constructed to evaluate the relationship between renal function and pharmacokinetic parameters. The intended result is a model that can successfully predict the pharmacokinetic behaviour, given information about renal function. Generally, this involves a regression approach in which renal function and the pharmacokinetic parameters are treated as continuous variables. One commonly used model is a linear relationship between GFR and CL/F or AUC of the drug. Other models (e.g. more mechanistic models) can be used if adequately supported by the data. The modelling results reported 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 for the drug and its active metabolites over a range of renal function).

IV.3 Development of Dosing Recommendations

The aim is to develop dosing recommendations that will decrease the overall variability in the population and ensure that the patients will obtain treatment that is effective and safe. Factors that should be taken into account are the intended use of the drug, the pharmacokinetic characteristics of the drug in renal impairment and the PK/PD relationship regarding efficacy and safety. Based on available information regarding PK/PD for efficacy and safety, target criteria should be specified a priori for what change in pharmacokinetics would justify a posology adjustment. Consideration should be given to possible differences in PK/PD relationship between patients with and without renal impairment. The target criteria should be based on the major concern (side effects or lack of efficacy) for the specific product. A thorough discussion of and justification for the chosen target as well as a description of how it was determined should be provided.

Study results including the graphical description and the model for the relationships between renal function and relevant pharmacokinetic parameters should be used to construct specific dosing recommendations. It is important that the recommendations are based on the complete data set using renal function as a continuous variable. Moreover, the variability in pharmacokinetics at different degrees of renal function as well as possible differences in variability between “normal” renal function and decreased renal function should be taken into account. 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. It should be noted that in case the phase III patient population has decreased renal function, e.g. elderly patients with mild renal impairment, the need for posology adjustment should be evaluated not only in patients with moderate and severe renal impairment but also in patients with normal renal function. Depending on when the renal impairment study is performed during the clinical development, the distribution of renal function in the phase III clinical trial patient population may not be known at the time of conducting and evaluating the renal impairment study. Although a preliminary dosage recommendation in renal impairment can be made based on the data obtained in the renal impairment study, the final evaluation and development of dosage recommendations in renal impairment may need to await finalisation of the phase III studies.

The cut-off(s) for posology adjustment(s) should be based on the data and are not necessarily restricted to the limits used to define the different renal function groups used for inclusion of subjects in the study. 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 for the drug or active metabolites in both ”normal” patients and patients with impaired renal function. It is often difficult to find a dosing regimen which would result in a comparable range of all pharmacokinetic parameters (AUC, C_{max}, C_{min}, time above minimum effective concentration etc.). Therefore, as already mentioned, it

is important that the specific characteristics of the compound are considered and that the parameters and target criteria chosen are justified. Simulations can be used to identify doses and dosing intervals that achieve that goal for patients with different degrees of renal impairment. In most cases it will not be sufficient to present the results of the simulation of only one dosage reduction regimen. Instead the relative merits of several combinations of dose- and dosing frequency-reductions in meeting the target criteria in the simulations should be discussed. This may be especially important if the pharmacokinetic target parameters for efficacy is known to be different from the most relevant parameter for safety. Another approach is to estimate appropriate cut-offs and doses given the information on pharmacokinetic parameters and distribution of renal function in the population. This approach can be used in cases where population pharmacokinetic studies are available and these have identified renal function as a covariate that influences the pharmacokinetics of the drug. With this approach, the most appropriate dosing strategy is estimated by minimising the total risk of deviation from the defined target.

A statistical analysis demonstrating that no dose adjustment is needed could be used in case of a reduced design and using an equivalence approach. In order to claim “no effect” of severe renal impairment, the 90% confidence interval for the ratio of PK measurements in severe renal impairment vs. the control group should be within predefined limits that should be based on the defined target criteria discussed above.

Regardless of whether specific dose reductions are recommended or not, simulations of the steady state exposure at the recommended dose(s) should be provided. The simulations should 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 versus renal function including appropriate measures for variability should also be supplied.

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 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 inhibition by e.g. concomitant medication could result in large increases in exposure.

V. LABELLING ISSUES

The information in the SPC 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. Even when no posology adjustment is needed, this should be stated in section 4.2. When creatinine clearance has been used to estimate renal function, this could be made clear in section 4.2.

Lack of information regarding influence of renal impairment on the pharmacokinetics could result in a contraindication (section 4.3) or warning (section 4.4) regarding e.g. severe renal impairment, depending on the characteristics of the drug.

Information regarding the influence of renal impairment 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. Also when pharmacokinetics in patients with renal impairment has not been evaluated, this information should be given in section 5.2. When

relevant, information that renal impairment is unlikely to affect the pharmacokinetics to a clinically relevant extent could be included in section 5.2, if this has been well justified.

In case a clear relationship is found between creatinine clearance 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).