1 24 May 2012
2 EMA/CHMP/203926/2012
3 Committee for Medicinal Products for Human Use (CHMP)

# 4 Concept paper on the need for revision of the Note for 5 guidance on the evaluation of the pharmacokinetics of 6 medicinal products in patients with impaired renal 7 function

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| Agreed by Pharmacokinetics Working Party | May 2012 |
| Adopted by CHMP for release for consultation | 24 May 2012 |
| Start of public consultation | 8 June 2012 |
| End of consultation (deadline for comments) | 31 July 2012 |

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9 The proposed guideline will replace 'The Note for guidance on the evaluation of the pharmacokinetics of
10 medicinal products in patients with impaired renal function (CHMP/EWP/225/02).

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

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| Keywords | *Pharmacokinetics, renal impairment, reduced renal function, special populations, clinical drug development, guideline, CHMP* |

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# 1. Introduction

The Note for guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function (CHMP/EWP/225/02) provides recommendations on when to conduct pharmacokinetic studies in patients with reduced renal function, design and evaluation of such studies and how to develop dosage recommendations in patients with renal impairment. This concept paper discusses the need to revise some sections of the guideline.

# 2. Problem statement

There is a need to update the Note for guidance regarding when to conduct studies in renal impairment.

# 3. Discussion (on the problem statement)

During recent years there have been several publications discussing the effect of renal impairment on non-renally eliminated substances (1-4). It has been reported that exposure can be significantly increased in patients with severe renal impairment also for products that are eliminated hepatically (5). Currently, the EU guideline recommends complete evaluation of the pharmacokinetics in renal impairment for substances that are primarily eliminated by renal routes. In addition, a study in severe renal impairment (reduced/staged design) is recommended for non-renally eliminated NTI substances. As end-stage renal disease may lead to large increases in AUC for some non-renally eliminated drugs, the EU recommendation might need to be revised to include non-NTI substances eliminated by non-renal routes.

The classification of renal function groups in the EU guideline differs from the National Kidney Foundation definition of stages of chronic kidney disease (6). As the classification of kidney disease in clinical practice within the EU seems to follow the National Kidney Foundation definition, it may be desirable to use the same cut-offs in the definition of renal function groups in the EU guideline.

Based on gained experience some additional minor issues have been identified that may be considered during the revision of the guideline. For example, the guideline could be updated with clarification and/or additional information on inclusion of patients on dialysis in renal impairment studies, on methods to determine renal function, on when to measure metabolites in the renal impairment study and on development of dosing recommendations.

# 4. Recommendation

A revision of the Note for guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function (CHMP/EWP/225/02) regarding the above-mentioned issues is recommended.

# 5. Proposed timetable

It is anticipated that a draft revision will be released 15 months after adoption of the Concept Paper. The public consultation on the draft revision will last for 6 months. Following the receipt of comments, the revision will be finalised within approximately 12 months

## 6. Resource requirements for preparation

The preparation will mainly involve the Pharmacokinetics Working Party (PKWP). It is anticipated that the document will be discussed at 4 PKWP meetings.

## 7. Impact assessment (anticipated)

The revised guideline will provide improved guidance for Pharmaceutical Industry and Regulatory Authorities that is in line with current knowledge and clinical practice.

## 8. Interested parties

Academia, international scientific societies (e.g. EUFEPS), pharmaceutical industry

## 9. References to literature, guidelines, etc.


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5. Zhang *et al*: Assessment of the impact of renal impairment on systemic exposure of new molecular entities: evaluation of recent dew drug applications. Clin Pharacol Ther. 2009; 85(3): 305-11
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