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Committee for Medicinal Products for Human Use (CHMP)

# Concept paper on the need to develop a reflection paper on development of medicinal products to prevent and treat acute kidney injury

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| Start of public consultation | 30 July 2018 |
| End of consultation (deadline for comments) | 31 July 2019 |

* The corrections concern: Section 2. Problem Statement, 'Scope', lines 49-51: addition of *include more precise specification of trial objectives using the estimand framework outlined in draft ICH E9(R1)*. Section 3. Discussion (on the problem statement), "Evaluation of efficacy", line 67: addition of *trial objectives, associated estimands and hence for*.

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

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| Keywords | acute kidney injury, renal failure, development |

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# 1. Introduction

Acute kidney injury (AKI) is a clinical syndrome defined by an acute decrease in kidney function that includes, but is not limited to, acute renal failure, and is the result of acute pathophysiologic processes. The pathophysiology of AKI is multifactorial and complex. It can occur as a consequence of various aetiologies, including specific kidney diseases; non-specific conditions; as well as extra-renal pathology, including medicinal product induced kidney toxicity and medical interventions.

Several classifications of AKI may apply, including concepts of volume responsive and volume – unresponsive conditions, and particular AKI staging systems which can be relevant to classify for severity of the syndrome and for short-term, medium-term and long-term risks. In addition, the chances of developing AKI after exposure to the same trigger differ among different individuals. This is attributed to a number of known and unknown susceptibility and confounding factors, which can vary widely between individuals.

The prevalence of AKI is increasing; especially in the elderly population. AKI is associated with short and long-term consequences. The disease burden has an impact on public health and there is obvious unmet medical need in development of medicinal products for prevention and/or treatment of AKI Currently there is no regulatory guidance on the development of medicinal products intended for prevention and/or treatment of AKI either on the EU or the ICH level available.

# 2. Problem statement

Several medicinal products have been evaluated with the aim either to prevent (such as statins, mannitol, melanocortin receptor agonists, atrial natriuretic peptide, pentoxiphylline, clonidine, saline, N-acetylcysteine, and fenoldopam) or to treat (such as alkaline phosphatase and dopamine) AKI or its complications, including long-term effects. In addition, there have been several attempts to develop clinical biomarkers to predict various outcomes of AKI. Despite these numerous efforts, no medicinal product has been centrally authorised in the EU up till now.

## *Scope*

Regulatory and scientific experience in the field of AKI from some of these activities provides the opportunity to summarise and consolidate agreed scientific advice in a guidance for development of medicinal products in various AKI settings.

The reflection paper will include discussion of and recommendations for the requirements for evaluation and development of medicinal products for the prevention and/or treatment of AKI and its long-term complications. Relevant topics for discussion include more precise specification of trial objectives using the estimand framework outlined in draft ICH E9(R1), patient populations, endpoints, study methodology, and study duration.

# 3. Discussion (on the problem statement)

## *Definitions*

Historically, various methods have been proposed in assessing AKI in clinical studies, i.e., Acute Kidney Injury (AKI) and Acute Renal Failure (ARF). From regulatory point of view, the choice of most suitable design depends on class of drug, the indication sought, duration of treatment. The reflection paper will address the proposed definitions for product development and further discuss these aspects:

## *Patient population and clinical setting*

Various clinical settings were used for the investigation of the prevention and the treatment of AKI such as patient undergoing (cardiovascular) surgery, or clinical settings used to investigate radiocontrast or sepsis induced AKI. The reflection paper will differentiate between the requirements for investigation of prevention and treatment of AKI. Enrolment criteria will be discussed to ensure the correct population is included in the study and to avoid misdiagnosis. Information will be provided on the type of disease setting suitable for investigation, the potential to extrapolate to broader target populations including high risk population. Feasibility to perform such studies will also be discussed.

## *Evaluation of efficacy*

Requirements for trial objectives, associated estimands and hence for the evaluation of efficacy of the new medicinal product will depend on the indication sought; i.e. prevention and/or treatment of AKI and its proposed duration of use. Specific requirements could apply for choosing the appropriate endpoints and methods to evaluate efficacy in relation to the assumed short-term, intermediate-term and long-term effects and whether the medicinal product is intended for prevention and/or treatment of AKI.

There is currently no consensus on the most appropriate study design with respect to duration of study, most valuable endpoints, and choice of comparator (placebo, SOC, particular medicinal product) to evaluate the efficacy for any specific proposed treatment and/or prevention indication for AKI.

The reflection paper will discuss methods to detect and monitor improvement and recovery of AKI, which may include measurement of serum creatinine (Scr), estimated GFR (eGFR), measured GFR (mGFR), urine output (UO), for specific intervals, and management of patients' follow-up. Several algorithms have been proposed to detect AKI based on SCr and urine output.

Clinical endpoints and their suitability for short-, intermediate- and long-term assessment, their appropriateness of use as primary and secondary endpoint for each setting and their clinical relevance will also be discussed. Endpoints of interest may include: incidence and duration of AKI; stage of AKI; incidence and duration of renal replacement therapy (RRT); All Cause Mortality (ACM); Major Adverse Kidney Events composite (MAKE), and Major Adverse Reno Cardiovascular Events composite (MARCE); incidence of AKI to CKD transition; length of ICU-stay; complete or partial recovery and non-recovery and sustained decline in renal function.

## *Requirements for assessment of safety*

The safety database should be adequate to characterise the safety profile of the product. Requirements for evaluation of specific adverse events, and reasonable follow-up periods will be part of the discussion in the reflection paper. This could include mortality, Major Adverse Kidney Events specific renal biomarkers, and/or other adverse effects.

## *Other methodological issues*

The reflection paper will discuss the important risk factors of AKI that could confound the results and the methods to mitigate them, including specific statistical analyses and stratification.

***Special populations.***

Issues specific to paediatric population will be discussed together with the settings where full or partial extrapolation may be possible. In case extrapolation is not possible, alternate strategies will be discussed.

# 4. Recommendation

The Rheumatology Immunology Working Party (RIWP) of the Committee for Human Medicinal Products (CHMP) recommends drafting a Reflection paper on development of medicinal products to prevent and treat acute kidney injury.

# 5. Proposed timetable

First draft of the reflection paper to be released for consultation by Q2 to Q3 2020.

Workshop with representatives from nephrology society and industry will be held after public consultation of the concept paper to address reasonable provisions to be included into the reflection paper.

# 6. Resource requirements for preparation

Development of the reflection paper will be led by the RIWP of the CHMP.

A multidisciplinary drafting group will be appointed with representation from the relevant parties including Committees or Working Parties, e.g. Scientific Advice Working Party (SAWP), Cardiovascular Working Party (CVWP) and Paediatric Committee (PDCO).

# 7. Impact assessment (anticipated)

Introduce into practice harmonised approaches for development and assessment of the products in the field.

# 8. Interested parties

Healthcare professionals, pharmaceutical industry, patient organisations, learned societies involved in kidney disease, renal and related research.

# 9. References to literature, guidelines, etc.

KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney International Supplements (2012) 2. 1; doi:10.1038/kisup.2012.1