European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CONCEPT PAPER ON THE NEED TO UPDATE THE NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE TREATMENT OF LIPID DISORDERS (CPMP/EWP/3020/03) AND THE NOTE FOR GUIDANCE ON THE CLINICAL INVESTIGATION ON MEDICINAL PRODUCTS IN THE TREATMENT OF HYPERTENSION (CPMP/EWP/238/95 REV. 2) TO DISCUSS THE NEED FOR OUTCOME STUDIES BASIS ON SAFETY DATA AT THE TIME OF MAA.

AGREED BY EFFICACY WORKING PARTY	8 June 2009
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	23 July 2009
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 October 2009

Comments should be provided using this template to ewpsecretariat@emea.europa.eu.

KEYWORDS	*Lipid lowering medicinal products, antihypertensive medicinal products, outcome studies, safety*

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

1. INTRODUCTION

Current CHMP recommendations for the clinical development of lipid lowering and blood pressure (BP) lowering agents accept the possibility of drug registration for the so called biological indications. This means that the basis for the demonstration of the efficacy of these drugs can be their effect on biological markers (LDL-cholesterol and BP respectively). Not being the intention of the CHMP to modify this policy, more clarity is needed to explicitly state where these principles would not be applicable and further data on the effect of these medicinal products on morbidity and mortality would be requested before a marketing authorisation is given.

2. PROBLEM STATEMENT

Both lipid-lowering and antihypertensive agents target cardiovascular risk factors (cholesterol levels and high BP) with no short-term symptomatic effect on patients. The final goal of these pharmacological strategies is to reduce cardiovascular mortality and morbidity by reducing the long-term impact of the cardiovascular risk factor they are targeting.

Use of the so called surrogate markers as proof of efficacy for drug approval has been in the past a matter of debate. Use and validation of biomarkers in drug development is encouraged, and may play a critical role in the early prediction of the effect of a drug in terms of both safety and efficacy. However, when it comes to criteria for approval, the foundation of the final proof of the efficacy on the effect on a particular surrogate may yield incomplete information for a sound benefit-risk assessment. Recent developments have raised additional doubts on the value of parameters such as HbA1c (antidiabetics) or serum cholesterol (lipid-lowering agents) as predictors of clinical benefit for patients. Whether the level BP decrease can quantitatively predict the clinical benefit of an antihypertensive agent disregarding other pharmacodynamic effects can be questioned as well.

Current CHMP recommendations for these types of drugs accept the use of biomarkers for the demonstration of the efficacy of these medicinal products, provided that the product information clearly highlights the limitation of the data. Indeed, in both documents it is stated that this situation would be acceptable provided that no suspicion on a detrimental effect on morbidity and mortality is found. The CHMP considers that these recommendations should be further detailed, in order to allow Applicants to anticipate in which situations outcome studies might be required before MA.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

It is proposed to revise and update the Note For Guidance On Clinical Investigation Of Medicinal Products In The Treatment Of Lipid Disorders (CMPM/EWP/3020/03) and The Note For Guidance On The Clinical Investigation On Medicinal Products In The Treatment Of Hypertension (CMPM/EWP/238/95 Rev. 2) in order to further discuss the following aspects:

1.- Type and level of detail of the clinical and non-clinical information expected for a proper evaluation of the safety profile of a new medicinal product in relation to key organs and systems (cardiovascular safety, renal safety, hepatic safety).

2.- Discussion on whether the quantity and quality of information should be different depending on the mechanism of action of the medicinal product in question (known class toxicity, new class of drugs).

3.- Suggest a safety evaluation algorithm that, taking into account the totality of the data, may help to establishing the need for outcome studies and the stage at which they will be required (pre- or post-licensing)

4. RECOMMENDATION

The EWP and its cardiovascular (EWP-CV) drafting group recommend the CHMP to consider a revision and update of the above mentioned guidelines in line with the criteria stated above.

5. PROPOSED TIMETABLE

It is anticipated that a draft document may be released 9 months after adoption of the final Concept Paper by the CHMP. The draft document will then be released for 6 months of external consultation and following the receipt of comments it will be finalised within approximately 3 months.

6. RESOURCE REQUIREMENTS FOR PREPARATION

The preparation will be done by the EWP-CV drafting group. One rapporteur from the EWP-CV drafting group will be involved for each document. The document is expected to be discussed on 3-4 EWP-CV drafting group meetings and on two EWP meetings.

In addition, a liaison with the Scientific Advise Working Party (SAWP) of the CHMP to revisit scientific advices given over the last years and an involvement of the Safety Working Party (SWP) of the CHMP may be required.

Involvement of the Scientific Advisory Group for Cardiovascular Issues (SAG-CV) before release for consultation and before final adoption is requested. External experts will be contacted when needed.

7. IMPACT ASSESSMENT (ANTICIPATED)

The document is intended to provide guidance to industry when performing trials to develop lipid-lowering and antihypertensive drugs. It should also provide a clear basis for the CHMP when assessing data and providing advice on these type of drugs.

8. INTERESTED PARTIES

European Society of Cardiology, European Federation of Pharmaceutical Industries and Associations (EFPIA)