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 NEED FOR REVISION OF (CHMP) NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE TREATMENT OF LIPID DISORDERS

AGREED BY EFFICACY WORKING PARTY	May 2008
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	30 May 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 August 2008

The proposed guideline will update note for guidance on Clinical Investigation of Medicinal Products in the Treatment of Lipid Disorders (CHMP/EWP/3020/03)

Comments should be provided using this template to EWPSecretariat@emea.europa.eu
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KEYWORDS	*CHMP, EMEA, drug evaluation, drug approval, guideline, lipid disorders*

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1. INTRODUCTION

Cardiovascular disease in general and ischaemic heart disease in particular is still one of the leading causes of death around the world. This is compounded by increasing incidence of diabetes and overweight leading to higher lipid levels and consequential atherosclerosis.

At present well established efficacy endpoints for cardiovascular drugs are effects on morbidity and mortality in patients with coronary artery disease. This requires large trials to demonstrate difference in clinical events (e.g., death and MI). Use of acceptable surrogate may reduce the number and duration of studies provided a clear link is established between surrogate end-points and clinical outcome.

A number of imaging techniques have been developed and some are standardised enough to be used in the drug development process. This may be particularly useful in early stages of development.

2. PROBLEM STATEMENT

Any imaging surrogate biomarker for atherosclerosis needs to:

- Measure changes in plaque volume/burden;
  and/or
- Measure changes in plaque composition;
- Be reproducible and repeatable;
- Correlate with clinical outcome.

According to ICH E9 the evidence of surrogacy depends upon a) the biological plausibility of the relationship, b) demonstration of prognostic value for the outcomes in epidemiological studies and c) clinical trial evidence that treatment effects on the surrogate correspond to effects on the clinical outcome.

While there is reasonable evidence for a) & b) the evidence of treatment effect & clinical correlation is not yet convincing.

A number of imaging techniques have been developed e.g., cIMT, IVS, QCA, MRI, PET, combined PET/MRI and SPECT. Some like cMIT and IVUS are standardised enough to be used in the drug development process. While clear correlation is still questioned, there is no doubt that information derived from these techniques is useful.

For new imaging techniques to be accepted, a validation of its results against the clinical outcome trials is necessary. Whether this link is generated from a large study combining CV outcomes and imaging techniques or from separate trials where the same type of treatment leads to changes in the same direction is matter for further discussion.

When the NfG on Clinical Investigation of Medicinal Products in the Treatment of Lipid Disorders was written, the data available was fairly limited. Since then these techniques have shown to provide increasingly useful information regarding vascular architecture, akin to that observed with coronary angiography. Since the document was written, FDA has accepted “lack of progression/regression of atherosclerosis” as indication for some lipid lowering products. In Europe such information has been accepted in section 5.1 of the SPC for some statins. As there is no guidance given in the document as to what is expected of these techniques and which methods are used, this causes confusion in interpretation of data submitted by the applicant.

The current wordings of section 2.3 and 3.3 could be improved and needs to incorporate this. It is proposed that sections 2.3 and 3.3 of the NfG are revised to expand on the acceptability of these techniques and give clear direction regarding the measurements data needed from these techniques to remove any ambiguity.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

The note for guidance needs to acknowledge the developing value of cardiovascular imaging modalities like cIMT, IVUS, MRI, PET, combined PET/MRI and SPECT. Of these cIMT and IVUS are sufficiently validated to be used in studies for regulatory submissions. The information derived from them, at present, could be particularly useful in early stages of drug development or dose finding studies.

Data generated by two techniques from two vascular beds is considered more robust for regulatory purpose.

Briefly the revision should include the following in sections 2.3 and 3.3:

1. cIMT

- Acceptance that this technique is sufficiently validated to be used in regulatory studies;
- Imaging measurement of common carotid and internal carotid arteries is possible by B-mode ultrasound and that because this is a non-invasive procedure it is possible to obtain serial measurements;
- Preferred primary endpoint - details about data acceptable for regulatory submissions e.g, measurements of both carotids including carotid bulb, 6 vs 12 segments, near/far wall etc. Details to be elucidated later;
- Secondary endpoints;
- Optimal standardisation of ultrasound machines at all sites.

2. IVUS

- Measures volume of atheroma in the arterial wall by combining a series of cross-sectional images of the vessel over a predefined length;
- Measurement details including requirement for all images to be interpreted by experienced technicians under supervision of a cardiologist blinded to treatment assignment;
- Reproducible IVUS landmarks and known pull back speed;
- Preferred primary endpoints – percent plaque volume (change from baseline) and/or plaque volume in most diseased 10 mm segment (change from baseline in mm and percent change.;
- Secondary endpoints – normalised total plaque volume (percent change), lumen diameter and any thickening.

4. RECOMMENDATION

The Efficacy Working Party recommends to that the NfG on Clinical Investigation of Medicinal Products in the Treatment of Lipid Disorders be revised to provide an updated EU regulatory point of view on issues related to cardiovascular imaging biomarkers.

The revision will apply to sections 2.3 and 3.3 of the current guideline and will include imaging modalities of cIMT and IVUS as stated above.

5. PROPOSED TIMETABLE

The concept paper, following adoption, will be released for 3 months consultation period.

It is anticipated that the draft revised CHMP guideline will be available 6 months after adoption of the concept paper. This will need to be released for 6months consultation period.

6. RESOURCE REQUIREMENTS FOR PREPARATION

No extra resource will be required for this. The document however will need to be discussed in the Cardiovascular Drafting Group and at the Efficacy Working Party, prior to finalisation.

7. IMPACT ASSESSMENT (ANTICIPATED)

The imaging techniques are expected to expedite the drug development by its use in early development phase for dose finding and proof of concept studies. Its subsequent value in phase III trials may provide supportive evidence of its therapeutic effect. There is no resource application to regulatory authorities and there is no additional burden on industry as it is already working on imaging techniques.

8. INTERESTED PARTIES

Professional bodies like European Society of Cardiology, British Cardiac Society and Royal College of Physicians need to be consulted once the revised NfG is ready to be released for consultation. The document will need to be discussed at the Cardiovascular Drafting Group and the EWP and opinion of CVS SAG may be needed.

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