EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the need for revision of the guideline of medical products used in weight control

Agreed by Cardiovascular Working Party	24 August 2012
Adoption by CHMP for release for consultation	20 September 2012[1]
Start of public consultation	1 October 2012[2]
End of consultation (deadline for comments)	31 December 2012[3]

The proposed guideline will replace the Guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96 Rev. 1).

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

Keywords	*Weight control, Obesity, Cardiovascular Risk*

[1] Last day of relevant Committee meeting.
[2] Date of publication on the EMA public website
[3] Last day of the month concerned.

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1. Introduction

The current guideline on medicinal products used in weight control (CPMP/EWP/281/96 Rev.1) was adopted by the CHMP 15. November 2007.
Since then the marketing authorisations of 2 weight-control medicinal products have been suspended in the EU due to cardiovascular and neuropsychiatric side effects. Further, requirements with regard to the impact of medicinal products for the treatment of diabetes on cardiovascular morbidity and mortality have been clarified and strengthened in the revision of the Guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus (CPMP/EWP/1080/00). Similar revisions are ongoing in some other guidelines which would also be relevant for products used in weight control.
In addition to weight reduction, the proposed indications of some medicinal products currently under assessment include claims with relation to maintenance of weight reduction. The expected data supporting this part of the indication needs further specification.
Given the dramatic worldwide increase of obesity and overweight, in depth evaluation of overall benefit/risk is a crucial issue. Thus, revisions of the requirements both with respect to efficacy and safety are warranted.

2. Problem statement and Discussion

Obesity is associated with an increased risk of cardiovascular morbidity and mortality and the final goal of pharmacological strategies is to reduce this risk. Even though intervention studies examining the association of weight reduction and cardiovascular events are lacking, obesity is generally accepted as a surrogate marker for increased cardiovascular risk. In this context, it should be discussed if a 5% weight reduction could be accepted as a primary endpoint. The current guideline states that there is no requirement to demonstrate a positive effect on cardiovascular mortality and morbidity prior to licensing, but this may not be true in all situations and it should be discussed when this would be necessary. Considering that the mechanism of action of some weight reducing agents may have a potentially negative influence on blood pressure, heart rate or other cardiovascular parameters, it would be essential to at least exclude a harmful effect before licensing. 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 marketing authorisation. The update would be firstly to ensure consistency with the requirements for antihypertensive, glucose and lipid lowering agents specifying different aspects of the assessment of cardiovascular safety depending on the mechanism of action and findings in pre clinical and clinical trials. Consistency with the other guidelines will, however, take into account the different target populations and the different objectives of treatments.

There are also several additional benefits not requiring long term treatment which can be of clinical relevance, e,g. beneficial effects on orthopaedic conditions, sleep apnoea and fertility. Therefore it should be considered in the context of the revision of this guideline whether more focus should be put on such efficacy endpoints.

Several weight reducing agents have a central mechanism of action, often targeting signaling pathways (e.g. serotonin and catecholamine pathways) involved also in the regulation of mood and temper. Considering that the risk of depressive conditions is increased in subjects with obesity, it is of utmost importance that the neuropsychiatric effects of the medical product are carefully described and monitored during the trials and that proposals for risk minimizing measures are developed.

Obesity is recognized as a chronic clinical condition that usually requires long-term therapy to induce and maintain weight loss. In the current guideline, a study duration of 1 year is expected, but it could be discussed if longer studies are needed, as well as the need for a randomized withdrawal design to fully evaluate the capability of the medical product to maintain weight reduction.

Further, introducing new criteria for identifying patients at high risk, e.g. the Edmonton Obesity Staging System, should be discussed.

The need for a run-in period in long term trials may be questioned and should be discussed in the context of the guideline revision.

Some sections of the current guideline referring to endocannabinoid neuromodulators may be not relevant anymore and should be considered to be deleted.

The EMA geriatric work plan aims to increase the representation of elderly patients in clinical trials. One tool to achieve this is to specify requirements in disease specific guidelines. This would be relevant also for the guideline on medical products used for weight control

3. Recommendation

The Cardiovascular Working Party (CVS WP) recommends the CHMP to consider a revision and update of the guideline of medical product used in weight control (CPMP/EWP/281/96 Rev. 1) including the following sections of the adopted guideline:

3.1 Introduction (background)

The section needs updating to reflect current scientific knowledge and development (especially concerning endocannabinoid neuromodulators).

3.2 Primary Endpoints

Clarification and updating of endpoints including cut-offs for relevant weight reduction

3.3 Secondary Endpoints

Updating of relevant endpoints including consideration of short-term beneficial effects.

3.4 Morbidity and Mortality

The current guideline states that there is no requirement to demonstrate a positive effect on cardiovascular mortality and morbidity prior to licensing but this may not be true in all situations and it should be discussed when this would be necessary.

3.5 Selection of Patients

New ways of identifying risk patients could be discussed.

3.6 Strategy and Design of Clinical studies

The need for a run-in period should be reconsidered.

Sections concerning duration of studies as well as other requirements supporting a maintenance indication (possibly requirement for randomized withdrawal design) should be updated.

The requirements concerning the representation of elderly patients should be updated.

3.7 Safety aspects

Requirements concerning the assessment of cardiovascular safety need to be included in line with the existing or pending updates of some other guidelines such as for glucose and lipid lowering medicinal products.

Requirements concerning the assessment and of neuropsychiatric safety, especially depressive syndromes, need to be updated and expanded.

4. Proposed timetable

It is anticipated that a draft document may be agreed by the CVS WP and adopted by the CHMP for release for consultation during the 1st half of 2013. 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.

5. Resource requirements for preparation

Cardiovascular Working Party

6. Impact assessment (anticipated)

The document is intended to provide guidance to Industry when performing trials to develop medicinal products indicated in weight control. It should also provide a clear basis for the CHMP when assessing data from studies for medicinal products in this indication and providing advice in this field.

7. Interested parties

The interested parties in the guideline include the industry (PhARMA, EFPIA and others), Academia, the European Society of Cardiology, the European Association for the Study of Diabetes (EASD), the European Association for the Study of Obesity (EASO), clinical trialists involved in weight control medicinal products and other Regulatory Agencies.

8. References to literature, guidelines, etc.

Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus. Committee for Medicinal Products for Human Use (CHMP). CPMP/EWP/1080/00 Rev. 1. Available at: http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500129256