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Guideline on clinical evaluation of medicinal products used in weight control

Draft

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This guideline replaces '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

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Table of contents

Executive summary

This guideline represents the second revision of the CPMP Guideline on clinical investigation of medicinal products used in Weight Control (CPMP/EWP/281/96). It is intended to provide guidance for the clinical evaluation of new medicinal products used to promote weight loss in obese adult patients. It clarifies the requirements for clinical documentation needed to support a marketing authorisation for weight loss, notably the recommended methods of assessing efficacy, selection of patients, strategy and design of clinical trials, safety aspects and overall strategy of development.

1. Introduction (background)

Obesity is recognized as a chronic clinical condition and is considered to be the result of interactions of genetic, metabolic, environmental and behavioural factors and is associated with increases in both morbidity and mortality. In general, health risks increase with severity of obesity and include hypertension, atherogenic dyslipidaemia, insulin resistance, type 2 diabetes mellitus and cardiovascular disease. The sleep apnoea syndrome, strongly associated with obesity, has an increased mortality. There is also an increased mortality from cancer in both men and women. Further, joint pain, urinary incontinence, impaired fertility, depression, anxiety and functional limitations, such as decreased mobility can severely impair quality of life.

According to the WHO, obesity may be expressed in terms of the Body Mass Index (BMI = bodyweight (kilograms) / height[metres^2]) with BMI between 18.5 and 24.9 representing the normal range, BMI 25 to 29.9 overweight, BMI ≥ 30 obesity while severe obesity is defined as BMI ≥ 40. The degree of obesity is of importance with respect to increased risk of morbidity and mortality. (Ref.: Flegal et al.) and the WHO defines different classes of obesity; class I BMI 30-34.9, class II 35 -39.9 and class III BMI ≥40. It should be remembered that these cut offs may differ in other, e.g. Asian, ethnic populations. Further, the presence or absence of other cardiovascular risk factors in addition to obesity also affects the expected risk of cardiovascular morbidity and mortality (Ref.: Hamer et al.). This should be taken into account when defining the most appropriate target population for pharmaceutical treatment.

Further, the location of body fat is also a predictor of the relative health hazards of obesity. High levels of central adiposity are known to be associated with increased risk of obesity related comorbidities and waist circumference has been shown to be an independent predictor of risk. A waist circumference of 94 cm or more for men and 80 cm or more for women is commonly used as an indicator of increased risk of obesity-related health problems, with 102 cm or more for men and 88 cm or more for women said to be indicative of substantially increased risk.

The general goals of weight loss and management are to reduce body weight and to maintain a lower body weight. Weight reduction has been associated with beneficial effects on cardiovascular risk factors such as blood pressure and lipid profiles as well as improved glycaemic control in both patients with and without type 2 diabetes. Relevant decreases in certain risk factors associated with obesity have been seen with loss of at least 5 to 10% of initial weight. Hence, one objective of weight loss in obese patients may be to reduce these risk factors, which, together with the obesity as such, otherwise most likely will lead to increased cardiovascular morbidity and mortality. As mentioned above, it should be taken into account that the benefit of decreases in certain risk factors associated with CV morbidity/mortality may differ between patient groups depending on degree of obesity as well as absence/presence of other risk factors.

Another aim of weight reduction is to reduce the prevalence and severity of other, non-cardiovascular related complications such as sleep apnoea, joint pain, urinary incontinence, impaired fertility, depression, anxiety and functional limitations, such as decreased mobility. Weight reduction with the aim to reduce obesity related complications during planned surgery (e.g. orthopedic surgery) could also be a significant benefit for patients.

Non-pharmacological options for treatment include nutritional education and modification (usually calorie restriction), behaviour modification, and increased activity and exercise. In severe obesity, very low calorie diets (VLCD) may be applied for a limited period of time and, finally, surgery as a last resort. **Pharmacological options** are not recommended until at least one trial of an appropriate weight-reducing diet has proved insufficient, i.e. inadequate initial weight loss was achieved or the individual, despite continuing dietary advice, could not maintain an initial weight loss. Pharmacological options are only considered as an adjunct to dietary measures and physical exercise.

In principle pharmacological options include the following:

- Centrally acting anorectic agents acting via catecholamine and/ or serotonin pathways. These drugs are associated with reduced subjective hunger ratings and reduced food intake.
- Drugs that inhibit the absorption of nutrients promoting weight loss without having a specific effect on appetite.
- Drugs that modulate incretin receptor activity, such as GLP-1 (glucagon-like protein 1) receptor agonists which act primarily via a reduction in food intake.

2. Scope

The scope of this guideline is restricted to the development of pharmacological options for treatment of obesity. Specific recommendations on non-pharmacological options are out of scope of this guideline.

3. Legal basis and relevant guidelines

This Guideline should be read in conjunction with the Annex I of Directive 2001/83/EC of the European Parliament and of the Council and European and ICH guidelines for conducting clinical trials, including those on:

- Pharmacokinetic Studies in Man (The Rules Governing Medicinal Products in the European Community, Vol III, 1989)
- Clinical Testing Requirements for Drugs for Long Term Use (The Rules Governing Medicinal Products in the European Community, Vol III, 1989)
- ICH Topic E9 Note for Guidance on statistical principles for clinical trials (CPMP/ICH/363/96)
- ICH Topic E1 guideline on the Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long Term Treatment in Non-Life-Threatening Conditions (CPMP/ICH/375/95)
- ICH Topic E4 guideline on Dose Response Information to Support Drug Registration (CPMP/ICH/378/95)
- Guideline on adjustment for baseline covariates (EMA/295050/2013)
- Points to Consider on Multiplicity Issues in Clinical Trials (CPMP/EWP/908/99)

- Guideline on Missing Data in Confirmatory Clinical Trials (EMA/CPMP/EWP/1776/99 Rev. 1)
- Guideline on the Investigation of Drug Interactions (CPMP/EWP/560/95/Rev. 1 Corr.*)
- ICH E7 Studies in Support of Special Populations: Geriatrics (CPMP/ICH/379/95) including Questions & Answers to ICH E7

4. Efficacy criteria and methods to assess efficacy

4.1. Introduction

Reduction of body weight should be the primary efficacy endpoint in the clinical studies. However, it should preferably be supported by clinically relevant effects on endpoints reflecting the beneficial effect of the documented weight loss.

4.2. Reduction of body weight and related variables

Baseline weight is the subject's weight at randomisation. Weight loss should be documented both as absolute weight loss (kg) and percentage weight loss relative to baseline body weight. Demonstration of a clinically significant degree of weight loss of at least 5- 10% of baseline weight, which is also at least 5% greater than that associated with placebo, is considered to be a valid primary efficacy criterion in clinical trials evaluating new anti-obesity drugs. Proportions of responders in the various treatment arms could be considered as an alternative primary efficacy criterion where response is more than 10% weight loss at the end of a 12-month period.

Proportions of responders with $\geq$ 5% weight loss should be documented as a secondary endpoint.

Further, the predictive value of weight loss after e.g. 3 months treatment with respect to long term effects should be documented in order to identify a population with expected long term benefit.

Measurements of central adiposity (e.g. waist circumference or waist to hip ratio) should always be documented.

Measurements using accepted and validated methods (i.e. DEXA, magnetic resonance imaging or computer tomography) should demonstrate that weight loss is associated with appropriate loss of body fat (as distinct from muscle or body water).

4.3. Cardiovascular risk factors

A new weight-lowering agent should in general show a neutral or beneficial effect on parameters associated with cardiovascular risk (e.g. blood glucose, blood pressure, lipid levels). The impact on the risk of the development of diabetes is considered as an important secondary endpoint. For specific claims with respect to beneficial effects on cardiovascular endpoints other than body weight, relevant guidelines should be followed.

4.4. Cardiovascular morbidity and mortality

For products that have shown clinically relevant weight reductions, there will be no requirement to demonstrate a direct positive effect on cardiovascular morbidity or mortality prior to licensing unless specific claims are made. Any claim of a reduction of cardiovascular morbidity and/or mortality will need to be supported by well-designed clinical trials that enrol a representative, "real world" sample of patients with obesity.

Studies aimed at excluding any detrimental effects on cardiovascular morbidity and/or mortality may be warranted in specific cases (see section 7.4.1).

4.5. Other weight related comorbidities

Assessment of the effect on comorbidities secondary to overweight/obesity such as sleep apnoea episodes, joint pain, urinary incontinence, impaired fertility, depression, anxiety and functional limitations, such as decreased mobility, is of high importance considering that these comorbidities may severely impact quality of life. Relevant and validated end points and symptom scores should be used to assess beneficial effects of the study drug on these co-morbidities.

5. Selection of patients

Patients eligible for pharmaceutical therapy should have a degree of obesity associated with a significant health risk.

Obesity should be diagnosed on the basis of a body mass index (BMI) of 30 kg/m2 or more in both males and females. For patients with multiple CV risk factors, a lower BMI at baseline could be considered. Considering that the risk of morbidity and mortality as well as other complications increases with increasing BMI, development programs should always include representative samples of patients with class II (BMI $\geq$35 kg/m2) and III obesity (BMI $\geq$40 kg/m2).

A relevant proportion of patients entering the studies should have coexisting cardiovascular risk factors in order to represent the expected target population.

6. Study design

6.1. Pharmacodynamics and pharmacokinetics

The mechanism of action of the drug should be established and discussed. It should be demonstrated that weight loss is associated with appropriate loss of fat.

Pharmacokinetic studies should be performed to characterize the disposition of the drug. Physiological changes associated with obesity and their effects on the distribution, protein binding, metabolism and renal excretion of drugs should be considered and investigated if considered relevant. Depending on the drug and its mode of action, relevant interactions (with for example antihypertensives, glucose lowering and lipid modifying agents) should be considered and investigated.

For detailed requirements, please see relevant PK guidelines.

6.2. Exploratory studies

Effective and safe dose regimens should be established in well-defined patient samples. In view of the potential for long-term treatment in this condition, it is particularly important to identify the lowest dose of the drug that safely achieves its therapeutic goal.

6.3. Confirmatory studies

Confirmatory phase III trials should be randomised, placebo controlled and double blind. Since weight control can be achieved by diet, exercise and behaviour modification alone, the use of a placebo group

is necessary to show clearly that the study drug and appropriate non-pharmacological interventions are more effective than the same non-pharmacological interventions alone. However, the use of placebo-controlled trials (particularly in long term studies) may be associated with a high rate of dropouts. This has been the case in many recent studies which has complicated the evaluation of the results. For this reason, an effective non-pharmacological intervention is warranted and the Applicant is urged to implement all possible measures to minimize the number of dropouts. Appropriate covariates should be included in the efficacy analyses, including but not limited to the baseline body weight. As long-term studies with effective drugs become available, it is recognized that actively-controlled trial designs may become appropriate in addition to placebo-controlled trials.

The need for a weight reducing diet run-in period will depend on the duration of the study. For studies with duration of 12 months or longer, this may not be necessary. For studies with $\leq$12 month duration, a run-in period in which all patients should be given similar instructions, advice and encouragement with regard to diet and behaviour modification and exercise should be implemented before randomisation. In long-term studies, such instruction and advice should be implemented at the start of the trial and reinforced at frequent intervals. The effect of other drugs on body weight (such as metformin, insulin, GLP-1 agonists) frequently prescribed in obese patients should also be taken into account.

Weight loss has often been observed to plateau after 5 to 6 months of continuous treatment with currently or previously available treatments, and therefore, at least 6 month duration of confirmatory trials is recommended to establish weight loss effect. However, at least one pivotal trial with duration of $\geq$ 12 month is expected in order to verify a beneficial effect on weight development and obesity related comorbidities. To support the duration of the weight lowering effect, a randomised withdrawal trial that allows assessment of weight development with and without continued treatment should be considered.

As obesity is a chronic condition, the possibility of different dose regimes, such as continuous or intermittent treatment should be considered.

It is essential that all trials should be designed to ensure that patients participating in these studies should have follow up examinations for a period deemed appropriate to assess withdrawal or rebound effects and the effect of drug cessation on appetite and weight control.

The duration of the clinical studies included in the application for a new drug may have impact on the recommended duration of treatment in the labelling. Further, for assessment of safety, longer exposure to the drug may be needed (see section 7.1).

Patients who fail to respond to treatment should be identified, as successful weight loss in the first months of treatment may predict long term effects. The predictive value of a range of % weight loss after e.g. 3 months treatment with respect to long term weight loss (e.g. after 12 months treatment) should be presented.

6.4. Studies in special groups

Studies should be designed to allow the applicant to identify and characterise any clinically important sub-groups (e.g. patients with comorbidities or risk factors) that respond to the treatment to a greater or lesser extent. E.g., it could be expected that patients with BMI class II/III may have a higher benefit of weight reduction with respect to reducing the risk of morbidity/mortality. If the indication is proposed to be limited to such sub-populations, they should be pre-specified in the protocol.

With regards to the characteristics of the trial population it should be considered that a relevant number of patients should be included from EU countries or countries with base line characteristics, lifestyle and non-pharmacological obesity interventions similar to those of EU member states.

Older patients

Concerning older patients, it should be considered that obesity may not necessarily have a negative effect on morbidity/mortality in older individuals. However, if the intended target population includes older patients, data should be presented for various age groups to assess the consistency of the treatment effect and safety profile in these patients in comparison with younger patient populations.

An addendum to this Guideline relates to clinical investigation of treatment of obesity in children (EMEA/CHMP/EWP/517497/2007).

7. Safety aspects

7.1. General considerations

Special efforts should be made to assess potential adverse reactions that are characteristic of the class of drug being investigated. Non-clinical data in relevant animal models evaluating the potential effect of the test drug on different safety aspects should be conducted and provided as an instrumental element of the safety evaluation as outlined in ICH guidelines (e.g. S7A and S7B).

In the clinical studies, an overall plan for the detection and evaluation of potential adverse events, including justification of the size and duration of the studies with respect to the possibility of detecting safety signals, should be prospectively designed early during the clinical development, optimally by the time of phase II studies. This program should take into consideration key elements of the primary and secondary pharmacology, as well as key toxicological findings from non-clinical studies.

Indications of increased risk of certain adverse events are an important concern and may trigger the request for additional specific long-term outcome trials (see also section 7.4.1).

7.2. Neuropsychiatric safety

In general, centrally acting anorectic agents have the potential to cause neuropsychiatric adverse events. Based on the mechanism of action the assessment of various neuropsychiatric adverse events may be relevant for such drug.

Prospective assessment of depression status and suicidality should be included in the clinical trial programme for all centrally acting agents, especially for those acting via serotonin pathways. Other psychiatric adverse events such as anxiety and insomnia should also be carefully assessed.

Especially for drugs acting on central catecholamine pathways, careful assessment of agitation, confusion, insomnia, nervousness, irritability, and psychotic reactions is recommended. Centrally acting anorectic agents may also cause cognitive adverse events such as attention disturbance, memory impairment and language disorders.

Well-validated scoring tools should be used to assess such neuropsychiatric adverse events.

To reflect clinical practice, subjects with a history of mild to moderate depression and those using anti-depressive treatment should not be excluded from the trials.

7.3. Abuse potential

Drugs acting through catecholamine pathways enhance catecholamine neurotransmission and usually have some stimulant and sympathomimetic activity. This euphoriant effect has been associated with potential for abuse. For these drugs, particular attention should be paid to the potential for drug abuse or dependence; withdrawal effects should be studied specifically. Where withdrawal effects are noted, therapeutic manoeuvres to reduce or minimize such effects should be investigated.

Drugs acting through serotonin pathways are not known to have a stimulant or euphoriant effect and thus have lower potential for abuse/dependence and withdrawal effects. However, this needs to be justified for each specific drug.

7.4. Cardiovascular safety

7.4.1. Cardiovascular disease

Considering that one of the potential aims of treatment of obesity is reduction of cardiovascular risk, weight-reducing drugs should not result in an increase of such a risk. It is therefore expected that the development programmes of these drugs provide sufficient information supporting the lack of excess of cardiovascular risk.

Type of studies

The complete development program, including non-clinical data (e.g. atherothrombotic findings, fluid retention, blood pressure, heart rate, renal function, electrolyte homeostasis, cardiac function, repolarisation and conduction abnormalities) will be taken into account in order to detect potential signals that may suggest an increased risk for cardiovascular events.

Concerning the clinical studies, two approaches are conceivable at the time of submission of the MAA to reliably exclude an increase in cardiovascular risk associated with the drug:

1. *A meta-analytic approach* with adequate size and mean duration (minimum of 12 months). A careful evaluation of the cardiovascular risk of the study drug based on available medical literature together with the absence of an increased cardiovascular risk in pre-clinical and clinical studies should be presented. A dedicated post-approval cardiovascular outcome study might not be necessary in such cases.
2. *A dedicated cardiovascular outcome study* with sufficient duration and power. This approach is favored whenever a cardiovascular safety concern is intrinsic in the molecule/mechanism of action or has emerged from pre-clinical or clinical studies and/or results from meta-analyses.

Study Population

In the development program, every effort should be undertaken to include a study population that mimics as much as possible the target population, regardless whether a meta-analytic or a dedicated outcome study approach is used. In either case, an adequate representation of high-risk patients, including subjects with cardiovascular risk factors (e.g. hypertension, hyperlipidemia), high risk for cardiovascular complications and confirmed history of ischaemic heart disease and/or congestive heart failure should be included.

Safety outcomes

The safety endpoint for the meta-analyses and outcome studies could be a composite of all major cardiovascular events (MACE): i.e. cardiovascular death, non-fatal myocardial infarction and stroke.

Hospitalisation for unstable angina, need for revascularization, heart failure or worsening of existent heart failure, TIA, and sudden death could also be included in a composite endpoint ("MACE plus"). It is important to ensure that these are all adjudicated events.

Additional parameters such as increase in body weight, oedema/fluid retention, occurrence of hypertension and heart rate/arrhythmias should also be systematically collected. Clinically relevant changes in cardiac function (e.g. by echocardiography) should be evaluated, if there is an indication of a detrimental effect on cardiac function.

Evaluation of the results

The overall results of the cardiovascular safety program (meta-analysis and/or dedicated outcome study) will always be assessed in terms of internal and external validity and in relation to the overall risk-benefit ratio of the drug. Acceptability of the data presented will be based on its overall quality, the point and interval estimates obtained for the calculation of the risk and the reliability of these estimations.

7.4.2. Valvulopathy and pulmonary hypertension

Cases of severe valvulopathy have been reported in patients undergoing therapy with certain centrally acting anorectic agents. Available data support that the mechanism of valvulopathy is attributed to specific agonism for the 5-HT2B receptor (Ref.: Rothman et al.) and therefore agents stimulating this receptor should be carefully assessed with respect to risk of this condition. This evaluation should include repeated echocardiography examinations (e.g. at baseline and every 6 months) in a relevant proportion of study participants.

Use of certain centrally acting anorectics has also been associated with an increased risk of pulmonary arterial hypertension. This should be taken into account in the development program.

Definitions

Overweight and Obesity are defined as abnormal or excessive fat accumulation that may impair health (WHO).

The WHO definition is:

- BMI greater than or equal to 25 is overweight
- BMI greater than or equal to 30 is obesity.

Body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. It is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m2).

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