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Guideline on clinical evaluation of medicinal products used in weight management

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Guideline on clinical evaluation of medicinal products used in weight management

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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 for weight management in overweight and obese adult patients. It clarifies the requirements for clinical documentation needed to support a marketing authorisation for weight management drugs, notably the recommended methods of assessing efficacy, selection of patients, strategy and design of clinical trials. The safety section was updated following finalisation of the Reflection paper on assessment of cardiovascular safety profile of medicinal products (EMA/CHMP/50549/2015).

1. Introduction (background)

Overweight and obesity are recognized as disease states that in some circumstances can develop into complications. They are considered to be the result of interactions of genetic, metabolic, environmental and behavioural factors and are associated with increases in both morbidity and mortality. In general, health risks increase with severity of overweight and obesity and include hypertension, dyslipidaemia, insulin resistance, type 2 diabetes mellitus and cardiovascular disease. Other symptoms and disease states that are related to overweight and obesity, such as sleep apnoea, joint pain, urinary incontinence, impaired fertility, depression, anxiety and functional limitations can also severely impair patients' health and quality of life.

According to the WHO, overweight and obesity may be expressed in terms of the Body Mass Index (BMI = bodyweight (kilograms) / height² [metres²]) with BMI between 25 and 29.9 kg/m² representing overweight, while obesity is defined as BMI \geq 30 kg/m². The degree of obesity is of importance with respect to the risk of morbidity and mortality, which has been shown to increase with increasing BMI (Ref.: Flegal et al.). The WHO defines different classes of obesity; class I (moderately obese) BMI 30-34.9 kg/m², class II (severely obese) BMI 35 -39.9 kg/m² and class III (very severely obese) BMI \geq 40 kg/m². It should be noted that these cut offs may differ by geographical region, as well as for individuals who do not have a typical body composition (e.g. highly muscular subjects).

The location of body fat is also a predictor of the relative health hazards of overweight and obesity. Central adiposity is known to be associated with increased risk of overweight and obesity related comorbidities and waist circumference has been shown to be an independent predictor of risk.

The main goals of weight 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 overweight and obesity have been seen with loss of 5 to 10% of initial weight and even a sustained weight loss of 3 to 5% is likely to result in health benefits (especially reductions in blood glucose, HbA1c and the risk of developing type 2 diabetes). Hence, one objective of weight management in overweight and obese patients is to reduce these risk factors, which contribute to increased cardiovascular morbidity and mortality. It should be taken into account that the benefit of decreases in certain risk factors associated with cardiovascular morbidity and mortality may differ between patient groups depending on the degree of overweight and obesity, as well as the absence or presence of other risk factors (Ref.: Hamer et al.).

Another aim of weight management could be a reduction of 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. Weight reduction with the aim to reduce

complications related to overweight or obesity during planned surgery (e.g. orthopedic surgery) could also be of significant benefit for patients.

Non-pharmacological treatment options for overweight and obesity 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, bariatric 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. adequate initial weight loss was not 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.

Pharmacological options may include drugs that regulate appetite via central (e.g. catecholamine and/or serotonin) and/or peripheral (e.g. GLP-1 receptor agonism) signalling pathways. Drugs that inhibit the absorption of nutrients, promoting weight loss without having a specific effect on appetite (e.g. orlistat), might also be used in the management of overweight and obese patients.

2. Scope

The scope of this guideline is restricted to the development of pharmacological options for weight management. 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
- Reflection paper on assessment of cardiovascular safety profile of medicinal products (EMA/CHMP/50549/2015)

4. Efficacy criteria and methods to assess efficacy

4.1. Primary efficacy endpoints

To document the effect of a product intended for weight management, reduction of body weight should be the primary efficacy endpoint in the pivotal clinical studies. It is important to be precise with respect to the trial objectives. In particular, during the course of follow-up, a relatively high proportion of patients will withdraw from randomised treatment or be lost-to-follow-up. Documenting the key scientific question of interest should include specification of the manner in which the measure of treatment effect will be made in light of these post-randomisation events. This specification can then, in turn, inform the trial design, data collection and choice of analysis method.

Placebo-corrected measurements of weight loss should be documented both as absolute and relative weight loss (kg and percentage) compared to body weight at randomisation and as responder analyses. Unless otherwise justified and agreed with regulators, it is appropriate to attempt to follow-up all patients for the duration of the trial to get a measure of weight change regardless of adherence to randomised treatment. Demonstration of a statistically significant, placebo-corrected weight loss of at least 5% of baseline weight after 12 months of treatment is a valid primary efficacy criterion. Responder definitions should include patients with at least 5 and 10% weight loss at the end of a 12-month period. Patients who discontinue from the trial before 12 months should be regarded as non-responders. Alternative analyses based on responder definitions that also consider other types of post-randomisation events as indicating non-response (withdrawal of randomised treatment, increase in the use of other interventions etc.) should be provided.

Clinically relevant effects on other endpoints reflecting the beneficial effect of the documented weight loss should preferably support the primary endpoint (see 4.2.2 and 4.2.3).

The predictive value of weight loss after short-term treatment (e.g. 12 weeks treatment on target treatment dose) with respect to long-term efficacy should be documented, in order to better identify a population with expected long-term benefit and include potential “stopping rules” for non-responders in the product label.

4.2. Secondary efficacy endpoints

4.2.1. Body weight related secondary endpoints

Measurements of central adiposity (e.g. waist circumference or waist to hip ratio) should be documented as secondary endpoints. Measurements using accepted and validated methods (i.e. DEXA, magnetic resonance imaging or computer tomography) should preferably be included as secondary endpoints to demonstrate that weight loss is associated with appropriate loss of body fat (as distinct from muscle or body water).

The maintenance of a reduced body weight following a low caloric diet (e.g. VLCD) could be an additional way to document the effect on weight management as a secondary outcome measurement.

4.2.2. Effect on cardiovascular risk factors and cardiovascular morbidity/mortality

The effect of treatment on parameters associated with cardiovascular risk (e.g. blood glucose, blood pressure, heart rate, lipid levels) should be documented and may be presented as responder analyses presenting proportion of patients with relevant improvements of these parameters. The impact on the risk of the development of type 2 diabetes is considered as an important secondary endpoint and should preferably be documented.

A new agent intended for weight management is expected to show a neutral or beneficial effect on parameters associated with cardiovascular risk.

For specific claims (i.e., inclusion in the wording of the indication) with respect to beneficial effects on cardiovascular endpoints other than body weight (e.g. treatment of type 2 diabetes, lowering of serum lipids), relevant guidelines for those conditions should be followed.

For products that have shown clinically relevant beneficial effects on weight management, 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 enrolling patients with overweight and/or obesity representative of the target population with respect to grade of overweight and obesity and baseline cardiovascular risk.

4.2.3. Effect on other weight related comorbidities

Assessment of the effect of weight reduction on comorbidities such as sleep apnoea, joint pain, urinary incontinence, impaired fertility, depression, anxiety and functional limitations, is of high importance and endpoints evaluating the effect on one or more of these comorbidities could be included as secondary efficacy outcomes. Relevant and validated end points and symptom scores should be used to assess any beneficial effects of the study drug on these co-morbidities. In addition, assessment and impact of weight reduction on quality of life should be documented using validated scores.

5. Selection of patients

Eligible patients are those for whom at least one trial of an appropriate weight-reducing diet has proven to be insufficient.

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 weight related risk factors, a lower BMI at baseline (e.g. ≥ 27 kg/m²) 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 relevant samples of patients with class II (BMI ≥ 35 kg/m²) and class III obesity (BMI ≥ 40 kg/m²) in order to describe the magnitude of the weight lowering effect in these subgroups.

A relevant proportion of patients with overweight and/or obesity enrolled into studies should have coexisting cardiovascular risk factors in order to represent the expected target population. The weight lowering effect as well as effect on glycaemic parameters should preferably be documented separately in patients with type 2 diabetes.

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. As for all therapeutic areas, it is important to identify the lowest dose of the drug that safely achieves its therapeutic goal. As overweight and obesity are chronic conditions, the possibility of different dose regimes, such as intermittent treatment could be considered.

6.3. Confirmatory studies

Confirmatory phase III trials should be randomised, placebo controlled and double blind. Since weight management can be achieved by diet, exercise and behaviour modification alone, the use of a placebo group is necessary to clearly show that the study drug on top of appropriate non-pharmacological interventions is more effective than the same non-pharmacological interventions alone. As new weight management drugs will become available in the EU, it is recognized that active-controlled trial designs may be relevant in addition to placebo-controlled trials.

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 and has complicated the evaluation of the results. For this reason, an effective non-pharmacological intervention is warranted and the sponsor is urged to implement all possible measures to minimize the number of dropouts, even when randomised treatment is discontinued. Before randomisation, all patients should be given similar instructions, advice and encouragement with regard to diet and behaviour modification. In long-term studies, such instruction and advice should be reinforced at frequent intervals.

Appropriate covariates should be included in the efficacy analyses, including but not limited to the baseline body weight. The effect of other drugs on body weight (e.g. metformin, insulin, GLP-1 agonists) frequently prescribed in obese patients should be considered.

Weight loss has often been observed to plateau after 5 to 6 months of continuous treatment with currently or previously available pharmacological treatments. However, at least 12 month duration of the majority of the confirmatory trials is recommended to fully document the effect on weight development and obesity related comorbidities. To document the effect on some weight related outcomes (e.g. delay in onset of type 2 diabetes), longer study durations may be needed while for others (e.g. effect on sleep apnoea) a shorter duration may be acceptable. A randomised withdrawal design, randomising patients on active drug to continue treatment or switch to placebo may give some useful information on the duration of the effect. 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).

6.4. Studies in special groups

Studies should be designed to allow the applicant to identify and characterise any clinically important sub-groups 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 countries.

With respect to the elderly, 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. Any limitation of the data set in this respect will be reflected in the product information.

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

7. Safety aspects

7.1. General considerations

Efforts should be made to comprehensively assess any potential adverse reactions that are characteristic of the class of drug being investigated.

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 safety 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 an additional dedicated long-term safety study before or after licensing (see also section 7.4).

7.2. Neuropsychiatric safety

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.

Some weight management drugs (e.g., those with a central mechanism of action) could have the potential to cause serious neuropsychiatric adverse events. If there are any indications of neuropsychiatric safety issues from mechanistic, non-clinical, early clinical or marketed drug data, then a prospective assessment of psychiatric, neurostimulant or cognitive adverse events (e.g. depression and suicidality, agitation, anxiety, insomnia, psychotic reactions, attention disturbances) should be performed.

7.3. Abuse potential and withdrawal effects

The potential for abuse/dependence and withdrawal effects needs to be justified for each specific drug. If there are any indications from mechanistic, non-clinical, early clinical or marketed data, then prospective assessment of abuse potential, dependence, and/or withdrawal effects should be performed. It is essential that trials have follow up examinations of a sufficient period to assess any potential withdrawal effects.

7.4. Cardiovascular safety

It is expected that the drug development programme, containing all relevant clinical and non-clinical data, adequately characterizes the cardiovascular safety profile enabling an evaluation of the cardiovascular safety in the marketing authorisation application. This refers in particular to products with a new mechanism of action or products belonging to a drug class for which the cardiovascular safety profile is not yet established or questioned, e.g. in case of a detrimental effect on another cardiovascular risk factor.

Requirements for the evaluation and quantification of the cardiovascular risk at the time of licensing are further outlined in the CHMP's Reflection paper on assessment of cardiovascular safety profile of medicinal products.

7.4.1. Valvulopathy and pulmonary hypertension

Cases of severe valvulopathy have been reported in patients undergoing therapy with certain centrally acting anorexigenic agents. Available data support that the mechanism of valvulopathy is attributed to specific agonism for the 5-HT_{2B} receptor (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 anorexigenics has also been associated with an increased risk of pulmonary arterial hypertension. This should also 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 kg/m² is overweight
- BMI greater than or equal to 30 kg/m² 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 of typical body composition. 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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