European Medicines Agency

---

**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

---

**GUIDELINE ON CLINICAL EVALUATION OF MEDICINAL PRODUCTS USED IN
WEIGHT CONTROL**

---

| | |
|---|---|
| **DRAFT AGREED BY THE EFFICACY WORKING PARTY** | July 2005 – April 2006 |
| **ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION** | 1 June 2006 |
| **END OF CONSULTATION (DEADLINE FOR COMMENTS)** | 30 November 2006 |
| **AGREED BY THE EFFICACY WORKING PARTY** | April – September 2007 |
| **ADOPTION BY CHMP** | 15 November 2007 |
| **DATE FOR COMING INTO EFFECT** | 31 May 2008 |

This guideline replaces CPMP/EWP/281/96

| **KEYWORDS** | *Obesity, guidance* |
|---|---|

## TABLE OF CONTENTS

**EXECUTIVE SUMMARY**

This guideline is a 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. An addendum to this guideline will relate to clinical investigation of treatment of obesity in children.

## 1.      INTRODUCTION (background)

Obesity is defined as a state of excess body fat that frequently results in impairment of health. According to the WHO it may be expressed in adults in terms of the Body Mass Index body mass index (BMI = bodyweight(kilograms) / (height[metres²])) with BMI of between 18.5 and 24.9 representing the normal range, a BMI of 25 to 29.9 representing overweight and a BMI of $\geq$ 30 considered to represent obesity. Severe obesity is defined as BMI of $\geq$ 40 and is associated with a substantially greater health risk than a BMI of 30.

Global cut-off points for overweight (BMI = 25.0 kg/m$^2$) and obesity (BMI = 30.0 kg/m$^2$) have been set by the WHO. Much debate has surrounded the appropriateness of these cut-off points in Asian populations and several studies in China, Japan, Taiwan and Hong Kong have reported an association between a BMI > 22.3 kg/m$^2$ and increased atherogenic risk factors. To promote healthy lifestyles and weight control, the WHO, the International Obesity Task Force and the International Association for the Study of Obesity have proposed lower cut-off points for overweight (BMI = 23.0 kg/m$^2$) and obesity (BMI = 25.0 kg/m$^2$) in Asian and Pacific Island Populations.

BMI appears to rise gradually during most of adult life, peaks at around 60 years, and then declines. After age 65, the rate of weight loss occurs at an average rate of 0 to 0.65 kg/year, although there is substantial individual variation. Loss of muscle mass begins from 30 to 40 years of age and continues into old age, while body fat increases through most of adulthood. Compared to younger individuals with the same BMI, older subjects tend to have a greater proportion of fat and an increased proportion of visceral and abdominal fat. An increase in intra-abdominal fat is associated with greater mortality in both younger and older adults, even when it is independent of overall adiposity. However, the effect of BMI on mortality seems to differ quantitatively between older and younger subjects and obesity may have less of an effect on mortality in older individuals than in younger individuals. In childhood, BMI is age and gender specific. BMI SDS (standard deviation score of patient's body mass index) is used to define childhood overweight and obesity. The BMI SDS is based on pooled international data that links the accepted adult cut-off points i.e. a BMI of 25 kg/m² for overweight and 30 kg/m² for obesity, to body mass index centiles for children while constructing bridging cut-off points related to age for children (see Paediatric Addendum).

Obesity is recognized as a chronic clinical condition that usually requires long-term therapy to induce and maintain weight loss and is considered to be the result of complex interaction of genetic, metabolic, environmental and behavioural factors, which are associated with increases in both morbidity and mortality.

Although the relationship is not linear, health risks increase with severity of obesity and include hypertension, atherogenic dyslipidaemia insulin resistance and type 2 diabetes mellitus, and cardiovascular disease (angina pectoris, claudication, venous thromboses and their major consequences such as pulmonary embolism). Obesity is associated with an increased risk of cardiovascular disease in adults and with less favourable cardiovascular risk factor status in children and adolescents. Obesity is also associated with an effect on cardiovascular morbidity and mortality, through association with hypertension, diabetes and dyslipidaemia.

The sleep apnoea syndrome, strongly associated with obesity, has an increased mortality. There is also an increased mortality from endometrial carcinoma in women and colorectal carcinoma in men. Hypertriglyceridaemia, reduced levels of high-density cholesterol, elevations of total and low-density cholesterol and abnormalities in haemostasis are also associated. Mechanical complications can severely impair quality of life. Obese patients have a significantly impaired quality of life, as

objectively measured by several independent tests. Overweight and obesity after young adulthood has also been associated with future risk of dementia. The most likely explanation for this is accelerated vascular dementia in heavier adults.

The location of body fat is also a predictor of the relative health hazards of obesity. Several epidemiological studies have shown that the regional distribution of body fat is a significant and independent risk factor for cardiovascular disease. Subjects with visceral (android/ abdominal) obesity with excess fat in the upper (central) body region, particularly the abdomen, represent a subgroup of obese individuals with the highest risk for cardiovascular disease and are also at greater risk of metabolic complications when compared to patients with lower body (gynoid) obesity with increased fat in the lower body segment, particularly the hips and thighs. Recently, waist circumference alone (measured at mid distance between the bottom of the rib cage and the iliac crest) has been found to be an integrated measure of obesity that is positively correlated with abdominal fat content and is an independent predictor of risk. There is a suggestion that change in waist circumference measurement has been shown to be a better correlate of change in visceral adipose tissue than change in waist hip ratio. There is no widely accepted clinical measure of central obesity in children.

Different measurements have been used to define distribution of fat, including skin-fold thickness, the ratio of circumference of waist to hip (waist to hip ratio WHR) or waist circumference alone. The technique of dual-energy x-ray absorptiometry (DEXA) has been shown to provide a direct, accurate, and precise measure of lean body mass and total fat mass, which allows quantification of fat mass in anatomically-defined regions of interest, and more precise evaluation of the impact of fat distribution. Other methods include computer tomography and magnetic resonance imaging.

The general goals of weight loss and management are to reduce body weight and to maintain a lower body weight over the long term.

**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 usually recommended until at least a trial of an appropriate 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.

Currently available pharmacological options include the following:

- Centrally acting anorectic agents
- Drugs that inhibit the absorption of nutrients
- Endocannabinoid neuromodulators

**Centrally acting anorectic agents** currently used in the treatment of obesity fall into three pharmacological categories: those that act via catecholamine pathways; those that act via serotonin pathways; and those acting via a combination of the two pathways. Drugs acting through catecholamine pathways enhance catecholamine neurotransmission, and usually have some stimulant and sympathomimetic activity. Although associated with reduced subjective hunger ratings and reduced food intake, their stimulant or euphoriant effect has been associated with potential for abuse. Drugs acting through serotonin pathways increase its release and reduce its re-uptake, and although they have no stimulant or euphoriant effect, they too may have associated neurotoxicity

Cases of severe, often fatal, pulmonary artery hypertension have been reported in patients undergoing therapy with certain centrally acting anorectic agents. This has been seen with the serotonin releasing agents, but not with the serotonin re-uptake inhibitors. An epidemiological study has shown that anorectic intake is a risk factor involved in the development of pulmonary artery hypertension and that the use of such anorectics is strongly associated with an increased risk for this adverse drug reaction. It has been shown that the duration of treatment greater than 3 months and a BMI of greater than 30 kg/m$^2$ increase the risk of developing pulmonary artery hypertension.

**Drugs that inhibit the absorption of nutrients** from the gastro-intestinal tract (and so promote weight loss without having a specific effect on appetite) are also available.

The **endocannabinoid neuromodulatory** system is involved in regulation of food intake and energy balance. Inhibition of the specific G-protein coupled with the cannabinoid -1 receptor (CB1) is another therapeutic option.

## 2    SCOPE

The scope of this guideline is restricted to the development of pharmacological options for treatment of obesity within the context of such options not usually being recommended until at least a trial of an appropriate non-pharmacological option has proved insufficient. Specific recommendations on non-pharmacological options are out of scope of this guideline.

## 3.    LEGAL BASIS

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)

- Biostatistical Methodology in Clinical Trials in Applications for Marketing Authorisations (The ICH Rules Governing Medicinal Products in the European Community, Vol III, addendum 3)

- 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)

- CHMP Note for Guidance on Clinical Investigation on Medicinal Products in the Treatment of Hypertension (CPMP/EWP/238/95 Rev. 2)

- CHMP Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Lipid Disorders (CPMP/EWP/3020/03)

- CHMP Note For Guidance on Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus  (CPMP/EWP/1080/00)

- Points to Consider on Adjustment of Baseline Covariates (CPMP/EWP/2863/99)

- Points to Consider on Multiplicity Issues in Clinical Trials (CPMP/EWP/908/99)

- Points to Consider on Missing Data (CPMP/EWP/1776/99)

- Investigation of Drug Interactions (CPMP/EWP/560/95)

- Obesity Research 12:440-441 (2004)

## 4    MAIN GUIDELINE TEXT

### 4.1    Specific considerations

#### 4.1.1    Need for placebo-controlled trials

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 drug and appropriate non-pharmacological treatments are more effective than the same non-pharmacological treatment alone. However, the use of placebo-controlled trials (particularly in long term studies) is often associated with a high rate of dropouts. For this reason, an effective non-pharmacological treatment is warranted to prevent

dropouts. In addition, the number of dropouts (for lack of efficacy) from the placebo group compared to the treatment group can provide useful information about the efficacy of the study drug. The reasons for drop out should be identified and reported. As long-term studies with effective drugs become available, it is recognized that alternative trial designs may become appropriate or acceptable.

## 4.2    Assessment of efficacy criteria

An important goal of the treatment of obesity is to prevent associated morbidity and mortality. Although no studies have as yet confirmed an effect on mortality or morbidity, weight reduction has been associated with reduction in blood pressure in both normotensive and hypertensive individuals, improvement in lipid profiles, and improved glycaemic control in both patients without diabetes and patients with 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, the main objective of promoting weight loss in obese patients is to reduce these risk factors, which otherwise ultimately lead to increased morbidity and mortality.

### 4.2.1    Primary endpoints

Weight loss is the primary endpoint. Demonstration of a clinically significant degree of weight loss of at least 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.

Weight loss should be documented both as absolute weight loss and by other appropriate measures (such as percentage body weight loss). Appropriate covariates should be included in the model, including but not limited to the baseline body weight, if clinically justified.

### 4.2.2    Secondary endpoints

Choice of secondary efficacy variables should be justified by the applicant and could include variables such as biochemical parameters of lipid and glucose metabolism as well as blood pressure, cardiac function, waist hip ratio, ultrasensitive C-reactive protein, sleep apnoea episodes and quality of life parameters.

An associated reduction in cardiovascular risk factor(s) is an important secondary end point (waist circumference). The maintenance of weight loss or the prevention of weight regain, after the plateau in weight has been reached, could also be considered as a secondary efficacy criterion.

## 4.3    Methods to assess efficacy

### 4.3.1    Measurement of weight loss

Baseline weight is the subject's weight at randomisation. Weight loss should be documented both as absolute weight loss and by other appropriate measures (such as percentage body weight loss). Appropriate covariates should be included in the model, including but not necessarily limited to the baseline body weight. A further illustration of the size of the treatment effect should be provided by looking at the proportions of responders in the various treatment arms -where response is more than 10% weight loss at the end of a 12-month period.

The difficulties of placebo controlled studies in obesity and the resulting high drop out rate should be considered in such discussions. It is important to follow up patients who have discontinued treatment to facilitate intention to treat analysis.

Measurements using accepted methods selected and justified by the applicant should demonstrate that weight loss is associated with appropriate loss of body fat (as distinct from muscle or body water). Measurement of changes in body composition and in fat distribution can be useful to better define weight loss.

Methods such as waist circumference measurement, waist to hip ratio, magnetic resonance imaging and computer tomography may be used to assess abdominal fat content.

Items to consider in assessing and discussing efficacy include the distinction between weight loss and maintenance of weight loss. The rate of weight loss may be determined by various factors (initial weight or degree of obesity, ideal body weight, duration of obesity) and has often been observed to

plateau after 5 to 6 months of continuous treatment with currently available treatments. An apparent reduction in drug effect may be associated with attainment of a more appropriate body weight or with a reduction in resting metabolic rate.

### 4.3.2    Risk factors

Cardiovascular risk factors associated with obesity (blood pressure, lipid profile, glucose homeostasis, fibrinogen) should be measured and monitored since weight reduction is usually associated with a rapid improvement of these parameters. Sleep apnoea episodes (and other disturbances of sleep wakefulness cycles), mechanical joint distress, infertility, psychosocial aspects (measured as quality of life) as well as other variables should also be considered. Improvement in one or more of these measurements can be considered as a secondary efficacy variable. For specific claims, relevant guidelines should be followed.

### 4.3.3    Morbidity and mortality

Effects on morbidity and mortality may be measured directly as efficacy variables, but can only be properly evaluated in large clinical trials. There is no requirement, however, to demonstrate a positive effect on these variables prior to licensing.

### 4.4    Selection of patients

Patients entering these studies should have a degree of obesity, which has been shown to be associated with a significant health risk and especially a risk of increased mortality. The study population will therefore depend on the degree of obesity and the presence of coexisting risk factors. Efficacy should be assessed in patients of both sexes.

Obesity in otherwise healthy adult patients should be diagnosed on the basis of a body mass index (BMI) of 30 or more in both males and females. Patients with associated or secondary effects of obesity (such as hypertension, hyperlipidaemia, diabetes mellitus or IGT/IFG, or cardiovascular disease), should be considered for such studies if BMI is greater than 25 (in the Caucasian population). Trials should be designed to take account of predictive risk factors of morbidity and mortality that include BMI, adipose tissue distribution (with an increased risk in the case of abdominal/android obesity), and association with other cardiovascular risk factors (such as smoking, diabetes or hypertension) and episodes of sleep apnoea. Prospective stratification for some of these factors may be appropriate.

### 4.5    Strategy and design of clinical trials

Confirmatory phase III trials should be randomised, placebo controlled and double blinded. When standard therapies are available, studies adding active controls may be necessary.

**Run-in period**: Patients enrolled in these trials should have been subjected to an appropriate weight reducing diet run-in period for a specified minimum time, and all patients should be given similar instructions, advice and encouragement with regard to diet and behaviour modification and exercise. It is important that exercise accompanies dietary changes as it has been shown to be important in promoting long-term maintenance of reduced weight. In long-term studies, such instruction and advice should be reinforced at frequent intervals. The effect of loss of diet compliance on weight control should be especially considered. The effect of other drugs (such as metformin) frequently prescribed in such patients should also be taken into account. The effect of smoking cessation and all changes in smoking habits on weight control should preferably be the object of special studies.

At present the optimum duration of treatment is unknown. To date all studies suggest an immediate cessation of treatment effect as soon as treatment is stopped. Long-term therapy for obesity is, therefore, likely to be required to show that weight loss can be achieved and maintained. Long-term studies are required to demonstrate treatment associated benefits and risks and are particularly useful in documenting any changes in or loss of drug effect. Since the physiological response to dieting and reduced food intake can suggest a reduction in drug effect, it is important to remember that drug effect can be continuing despite a reduction in the rate of weight loss and may even be manifest as a failure to regain weight lost.

At present, trials documenting the effect of treatment for at least one year are required but an applicant intending to demonstrate the effect of weight loss on morbidity and mortality would require a longer prospective study.

### 4.5.1    Pharmacodynamics

Although there are no specific requirements for pharmacodynamic testing, the mechanism of action of the drug should be established and discussed in relation to that of relevant drugs already available. The monitoring of adverse events related to the pharmacodynamics of the studies drug should be conducted according to the existing ICH guidelines.

### 4.5.2    Pharmacokinetics

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.

### 4.5.3    Interactions

Depending on the drug and its mode of action, relevant interactions (with for example antihypertensives) should be considered and investigated. Since obese patients exhibit varying degrees of glucose intolerance, the possibility of interactions with oral hypoglycaemic agents should be considered.

Bias introduced by concomitant medication should be recognized and controlled as far as possible in control and active groups.

### 4.5.4    Exploratory studies

Effective and safe dose regimens should be established in well-defined patient samples. It should be conclusively demonstrated that weight loss is associated with appropriate loss of fat. 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.

### 4.5.5    Confirmatory studies

Large clinical trials should be performed in patients with well-defined obesity to demonstrate efficacy and safety with long-term use. Although effective use of anorectic agents or weight control agents has been associated with positive effects on risk factors such as reduced blood pressure, improved lipid profiles and improved glycaemic control, studies to demonstrate effects on long term morbidity and mortality have not yet been done. 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 of withdrawal or rebound effects and the effect of drug cessation on appetite and weight control.

As obesity is a chronic condition, the possibility of different dose regimes, such as continuous or intermittent treatment or use in combination with other anorectic agents, should be considered and explored. Additional factors to examine could include evidence of potential for drug abuse or dependence, and patterns of weight gain associated with cessation of dosing. 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. If any claims are to be made with respect to such sub-groups, they should be pre-identified in the protocol.

Patients who fail to respond to treatment should be identified as studies to date suggest that successful weight loss in the first month of treatment may predict ultimate success in weight loss.

### 4.5.6    Studies in special groups

An addendum to this Guideline will relate to clinical investigation of treatment of obesity in children.

Studies in the elderly should consider that the effect of BMI (an index of total body fat) on mortality seems to differ quantitatively between older and younger subjects, and obesity may have less of an effect on mortality in older individuals than in younger individuals.

### 4.6 Safety aspects

#### 4.6.1 General considerations

As it is likely that effective use of drugs used in weight control will require intermittent or long-term use, it is important that all adverse events occurring during the course of clinical trials should be fully documented with separate analysis of adverse drug reactions, drop-outs, and patients who died on therapy. Adverse drug reactions should be characterised in relation to duration of treatment, dose regimen, and initial body weight or pattern of obesity, i.e. truncal or general obesity.

In view of the goals of treatment of obesity, drugs used to treat it should be shown to have no deleterious effects on cardiovascular risk factors.

Special efforts should be made to assess potential adverse effects reactions (especially cardiovascular and neuro-psychiatric) that are characteristic of the class of drug being investigated. Adverse reactions characteristic of drugs acting on central catecholamine pathways reflect their sympathomimetic and stimulant properties and include reactions of early onset (agitation, confusion, insomnia, nervousness, and irritability) and reactions that tend to occur during long-term use (psychotic reactions). Adverse reactions reported with drugs acting on central serotonin pathways include gastrointestinal disturbance, drowsiness, dizziness, insomnia and depression (especially during long-term use).

Cases of pulmonary artery hypertension have been reported in patients who have received certain centrally acting anorectics In these cases, treatment duration of greater than three months and the level of the BMI (>30) increased the risk. Although the absolute risk of pulmonary hypertension attributable to the use of these drugs is small, this association should be kept in mind in studies to determine the risk-benefit ratio of long-term drug treatment and increased vigilance with regard to this complication should be exercised in both drug development and post marketing studies.

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.

The ICH/EU E1A guideline (Extent of Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions) should be followed in addition to other relevant guidance.

#### 4.6.2 Interactions

Obese patients often have associated risk factors, for which they are receiving multiple therapies, resulting in increased probability of interaction. Depending on the mechanism of action and based on the results of non-clinical data and previously conducted clinical trials, possible safety concerns arising from PK or PD interactions with commonly co-prescribed medications should be investigated in phase III studies.