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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON CLINICAL EVALUATION OF MEDICINAL PRODUCTS USED IN WEIGHT CONTROL (CPMP/EWP/281/96 Rev. 1)

ADDENDUM ON WEIGHT CONTROL IN CHILDREN

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ADDENDUM ON WEIGHT CONTROL IN CHILDREN

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1. INTRODUCTION (BACKGROUND)

This document is an addendum to the Guideline on Clinical Investigation of Medicinal Products used in Weight Control for Adults[1]. It provides guidance on the clinical investigation of medicinal products used in weight control in the paediatric population and should be read in conjunction with the Annex I to Directive 2001/83/EC, as amended, and with relevant European or ICH guidelines for conducting clinical trials, as outlined in the adult guideline.

The prevalence of child obesity is increasing rapidly on a global scale. It is a serious issue with many health and social consequences that often continue into adulthood. Obesity occurs when an individual takes in more energy than they expend although some people may be genetically more susceptible than others. The rise in obesity has been too rapid to be solely attributable to genetic factors and thus must reflect changes in eating patterns and levels of physical activity. It is especially prevalent in industrialised countries where sedentary lifestyles are commonly coupled with high consumption of convenience foods.

Obesity is associated with a range of co-morbidities including type 2 diabetes or hyperinsulinaemia, hypertension, dyslipidaemia and social and psychological problems including stigmatisation, discrimination and prejudice. Coronary heart disease, cancers and joint and bone pain are co-morbidities that are well documented in adult obesity, with coronary heart disease being the most common cause of premature death among obese people. Less clear are the links between cancer and obesity. The evidence is strongest for colon cancer where the risk is nearly three times higher in obese men and women.

As childhood obesity frequently continues into adulthood as described above, obesity in childhood is a risk factor for all of the above disease states in later life.

2. DEFINITION OF OBESITY IN CHILDREN

A wide variety of definitions for childhood obesity are in use, but a universally employed definition does not, however, exist. The body mass index (BMI = bodyweight (kilograms)/ (height [metres^2]) is widely used in adult populations and a 30 kg/m^2 cut-off point is recognised internationally as a definition of adult obesity.

However, in children the situation is more complex as the BMI changes substantially with age. BMI SDS (standard deviation score of patient's body mass index) is used to define childhood overweight and obesity in this guideline. The BMI SDS is based on pooled international data that links the accepted adult cut-off points, a BMI of 25 kg/m^2 for overweight and 30 kg/m^2 for obesity, to body mass index centiles for children while constructing bridging cut-off points related to age for children[2]. Primary obesity is obesity due to primary causes including lifestyle and dietary habits coupled with lack of adequate physical activity. Secondary obesity refers to obesity where there may be an underlying medical condition such as chromosomal disorders, endocrine disorders or metabolic disorders.

3. AGE CLASSIFICATION

The ICH guidance document[3] on clinical investigation of medicinal products in the paediatric population uses the following categorisation for age classification of paediatric patients:

Ages are defined in completed days, months, or years.

- preterm newborn infants
- term newborn infants (0 to 27 days)
- infants and toddlers (28 days to 23 months)
- children (2 to 11 years)
- adolescents (12 to 16-18 years (dependent on region))

It is recognised, however, that there is considerable overlap in developmental (e.g., physical, cognitive, and psychosocial) issues across the age categories.

In this guideline the following two categories are used to define subgroups of the paediatric population: 1.Younger children, and 2. Adolescents, categorised as follows:

1. Younger children: age from 6 to 10 years (or puberty) for girls and 6 to 12 years (or puberty) for boys
2. Adolescents: age from 10 years (or puberty) to 18 years for girls and from 12 years (or puberty) to 18 years for boys

For children aged 2 years to 6 years it is recommended that weight loss be attained through lifestyle modification only.

4. TRIAL POPULATIONS

Studies in children, whose age is determined by the proposed indication, are required.

In general the results of studies in adults cannot be extrapolated to adolescents or from adolescents to younger children. Study results from weight loss trials outside Europe could, however, be extrapolated to the European population since efficacy in terms of weight loss is not dependent on any ethnic background. Justification should be provided for using extrapolation data. Lifestyle factors may, however, have an important effect on efficacy in that a drug may be more effective in some populations with, for example, a low degree of physical activity and this should be considered in performing trials. The population studied should largely reflect the population intended for treatment in real life.

4.1 Non-pharmacological measures

Design of clinical trials on obesity in children should include, and precisely define, all types of intervention (lifestyle changes, diet, physical activity, parental involvement). As discussed below, trials should consist of three phases: a run-in phase; an active treatment phase; and a follow-up phase. The run-in period (without any medication) should last 3 to 6 months. All non-pharmacological interventions should begin in the run-in phase and continue during the blind treatment phase and during the follow-up phase. Relevant details about the medical history of the patient and the family should be collected and all co-morbidities well documented before enrolling the child into the trial. Any approach to specific interventions should be justified and the interventions proposed should be relevant and appropriate for the target population and not only for the trial purposes. As described above, two populations of children should be differentiated: younger children and adolescents. It is recognised that clear cut-off points for these two groups of patients are difficult to define and that there will be some overlap in the two age groups in terms of puberty.

4.2 Surgical interventions in obesity in children

Surgical intervention is normally restricted to adults. It is considered to be a last resort therapy. While it is acknowledged that comparison studies between surgical intervention and medical intervention might be useful, at present too little data are available to recommend such a design.

4.3 Goals of pharmacotherapy in obesity in children

Pharmacotherapy is only one aspect of a weight loss regimen. Pharmacological treatment of childhood and adolescent obesity and whether treatment translates into less obesity and/or less morbidity in later life is poorly understood.

Treatment goals are composite and need to encompass age, stage of growth and development, degree of overweight and the presence of associated co-morbidities. Halting abnormal/excess weight gain or decreasing the rate of weight gain are important goals in paediatrics and could be primary endpoints. For those subjects with obesity related complications weight loss is a primary endpoint.

4.4 Design of clinical studies in the development of medicinal products for the treatment of obesity in children

Pivotal trials should preferably be conducted by physicians experienced in the management of childhood obesity. They should be performed in centres with access to the relevant multidisciplinary

teams that can provide expertise in drug monitoring, diet, psychological support, behavioural interventions and physical activity.

Inclusion criteria: It is recommended that separate trials for younger children (6 years to puberty) versus adolescent children (puberty to 18 years) are performed. This is because of the considerable physiological changes in body composition, metabolic responses and behaviour occurring during puberty. Patients should be obese and have a documented history of failing to lose weight by means of lifestyle modification, before enrolment into the pharmacological phase of a study. After the run-in phase, study participants who do not have associated co-morbidities should not enter the active phase of the study if the results of the non-medicinal interventions suggest adequate weight loss (they no longer fulfil the definition of obesity). Conversely, those participants free of any co-morbidity should be enrolled if the run-in phase did not result in significant weight reduction. Children or adolescents with severe obesity should enter the active phase of the trial irrespective of the weight changes obtained during the run-in phase when at least one of the co-morbidities exists. Children of all ages should be equally represented in the study.

In the case of co-morbidities or parental obesity the BMI SDS threshold for study inclusion could be lowered.

Exclusion criteria: patients with secondary causes of childhood obesity such as mental retardation, chromosomal problems or syndromic obesity (e.g. Prader-Willi syndrome) should be excluded from the pivotal trials. Separate trials are needed for children with secondary causes of obesity. It is recommended that subjects suffering from severe co-morbidities be excluded from pivotal trials. This is because these severely obese children may require more intense medical management than is available in clinical trial conditions. Patients who have undergone any surgical intervention for the management of obesity e.g. bariatric surgery should also be excluded from a trial because this intervention may affect outcome. Conversely, adolescents who have responded well in the suggested minimal 3 to 6 months run-in period should not be excluded unless they are no longer obese. Patients with confirmed bulimia nervosa disorder should be excluded from trials.

4.5 Trial methodology

Trials should be randomised, double-blind, placebo-controlled trials. There should be a run-in phase, followed after randomisation by a blinded treatment phase and follow-up. Non-pharmacological interventions (lifestyle changes, dietary manipulation, physical activity etc.) should be standardised and remain unchanged during all three phases of the study. The use of food questionnaires could be considered in special cases although it is considered that the standardisation of food intake is not feasible and the reproducibility of such studies is relatively low.

The treatment phase should last for at least 1 year, as stabilisation of the effect is needed. As with adults, the problem of drop outs is recognised in both the placebo and active treatment groups. Historically there have been high rates of premature subject withdrawal in trials of medicinal products used in the management of overweight and obesity. Every effort should be made to follow-up these patients fully and include them in the intention to treat analysis. Patients should be seen on a regular basis and their weight monitored at baseline and at final analysis. If possible, patients who drop out from a 1 year study should have a body weight measurement at the time he or she would have completed the study after 1 year of taking part.

After discontinuation from the study the patients must be followed to assess maintenance of effect and any evidence for relapse and/or rebound. It is recommended that the observation phase after stopping drug therapy should last 6 months at least.

The applicant should indicate how he proposes to ensure the long-term follow-up of possible adverse reactions to the use of the medicinal product and efficacy in the paediatric population as outlined in Paediatric Regulations.

The possibility of an excessive pharmacodynamic effect, e.g. excessive weight loss, is unlikely and would relate to dose problems rather than to the duration of the study. In the case where investigators would like to conduct studies of shortened duration scientific advice should be sought.

DEXA scanning might be appropriate in a representative sample of trial patients to ensure that any weight reduction is caused primarily by a reduction in fat content and not lean-body mass.

5. ASSESSMENT OF EFFICACY OF NEW MEDICINAL PRODUCTS FOR THE TREATMENT OF OBESITY IN CHILDREN

It is recommended that the primary endpoint is a change in BMI SDS[2] as described in the definition of obesity in children above. In adults a 10% weight reduction is accepted as a positive endpoint. However the degree of change should be justified by the applicant.

While it is important to obtain statistically significant results, it is also important to consider clinical significance defined via the responders' rate. Research in this area is encouraged. In the meantime, justification should be provided for all design approaches to show clinically relevant effects.

Parameters relating to co-morbidities are secondary endpoints and can include improved glucose control, improved lipid profile, enhanced exercise tolerance, better mental health and/or quality of life, reduced use of adjunct medications etc. Choice of endpoints should be justified.

Behavioural changes are considered as secondary endpoints. Validated psychological tools must be used and justification for their use should be provided.

6. ASSESSMENT OF SAFETY OF THE NEW MEDICINAL PRODUCTS FOR THE TREATMENT OF OBESITY IN CHILDREN

Safety aspects are dependent on the mechanism of action of the investigational medicinal product. Appropriate safety data should be collected during the entire drug treatment period, which will usually be at least one year, and for the duration of the follow-up period. This data should notably encompass the adverse events related to lipid profile, liver function, cardiovascular system function and rebound phenomenon. For centrally-acting anorectic agents, in particular, it is recommended that special attention and monitoring is afforded to neuropsychiatric events such as depression, sleep pattern and nightmares, assessment of self-esteem, aggression or suicidality. Although self-esteem could fall under the efficacy category it is more appropriate to monitor it as a safety issue.

In growing children growth parameters should also be monitored in addition to standard safety evaluations specific to growing children such as assessment of Tanner stage at baseline and endpoint.

For centrally-acting anorectic agents the abuse potential should be considered and factored into trial design in an appropriate manner. This is especially important in the adolescent age group.

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