



12 December 2014



## Medicinal products used in weight control: first, do no harm

### ***Submission of comments on 'EMA Guideline on clinical evaluation of medicinal products used in weight control' (EMA/CHMP/311805/2014)***

#### **Comments from:**

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#### **Summary of our comments:**

- The draft guideline on evaluation of the harm-benefit balance of medicinal products used in weight control, released for consultation by the EMA in July 2014, contains a number of improvements over the existing version, adopted in 2007, in particular the recommendation to systematically assess the neuropsychiatric and cardiovascular adverse effects of drugs that act on the central nervous system.
- However, in the draft guideline, the Committee for Medicinal Products for Human Use (CHMP) accepts that evaluation of the efficacy of weight-control drugs can be based on modest weight loss alone after one year only, a surrogate endpoint that has not been demonstrated to translate into a reduction in morbidity and mortality. Instead, *Prescrire* argues that in order to determine whether treatment effects are maintained, it is essential to conduct clinical trials with a follow-up of at least several years prior to submission of the marketing authorisation (MA) application.
- In addition, the draft guideline recommends “actively-controlled” trials but does not specify that non-pharmacological therapies should be preferred (dietary and/or psychological/behavioural support, gastric banding or the use of another established medical device). Moreover, based on numerous disasters with amphetamine anorectics, these drugs should be avoided due to their foreseeable unfavourable harm-benefit balance
- Regarding the evaluation of adverse effects, *Prescrire* urges the EMA to broaden its recommendation to assess neuropsychiatric and cardiovascular adverse effects to include all medicinal products used in weight control, regardless of their mechanism of action, and also to systematically evaluate:
  - the adverse effects of rapid weight loss, including increased fracture risk;
  - the adverse effects already known to occur with other weight-control drugs;
  - the risk of interaction with other drugs likely to be used by overweight patients (antidiabetic drugs, antidepressants);
  - the risk of addiction to weight-control medicines, since they are often prescribed for patients who would be particularly susceptible (eating disorders).
- In order to take on board the lessons learnt from past public health disasters caused by appetite suppressants, *Prescrire* also insists that enhanced surveillance of the adverse effects of weight-control medicines is necessary for at least 5 years post-authorisation, but that these post-authorisation “safety” studies must not be used as a pretext for approving dangerous, under-evaluated medicines, nor to keep dangerous medicines on the market pending the results of these studies.





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#### **1. General comments**

Stakeholder number <i>(To be completed by the Agency)</i>	General comment (if any)	Outcome (if applicable) <i>(To be completed by the Agency)</i>
	<p><b>In its response to the EMA consultation, <i>Prescrire</i> insists on the need to use morbidity and mortality endpoints to evaluate whether or not the effects on weight translate into improved prognosis, and on the need for proactive, intensive monitoring of adverse drug reactions.</b></p> <p>In July 2014, the Committee for Medicinal Products for Human Use (CHMP) released for public consultation its proposed revision of the guideline on clinical evaluation of medicinal products used in weight control (1).</p> <p>The current consultation follows a previous consultation organised by the EMA in late 2012 on the need for revision of the existing guideline, to which <i>Prescrire</i> responded (2,3).</p> <p><i>Prescrire</i> reminded the EMA of the importance of the principle: “first, do no harm”, in particular insisting that evaluation of the efficacy of these medicines should be based on demonstration of a reduction in morbidity and mortality, and not simply on modest weight loss. <i>Prescrire</i> also urged the EMA to take into account the risk of these drugs being abused and used as non-essential dieting aids, and to actively look for adverse effects (in particular</p>	

cardiovascular and neuropsychiatric adverse effects), especially with drugs with appetite suppressant properties (3).

As of 2014 there are many weight-control medicines in the pipeline, some at a very advanced stage of development, such as *liraglutide* (Saxendu<sup>®</sup>) and the fixed-dose combination of the amphetamine-like *bupropion* (also known as *amfebutamone*) and *naltrexone*. This situation makes a revision of the guideline particularly urgent, so that the CHMP can produce robust recommendations to protect patients from dangerous medicinal products when the pharmaceutical companies apply for marketing authorisation (MA). In particular, *Prescrire* would like to draw the CHMP's attention to the need to be especially vigilant when evaluating requests to add the treatment of obesity as a new indication for medicinal products that have already been approved for other indications.

The draft guideline released for consultation by the EMA contains a number of improvements over the existing version, adopted in 2007, that will mean that harm-benefit evaluations of medicinal products used in weight control will better meet the needs of patients and healthcare professionals (1,4). However, a number of *Prescrire's* original comments remain unaddressed or have been insufficiently addressed.

### **Efficacy must be based on demonstration of a reduction in morbidity and mortality, rather than on modest weight loss alone**

The introduction section of the draft guideline states: *"Relevant decreases in certain risk factors associated with obesity have been seen with loss of at least 5 to 10 % of initial weight"*. This statement might be supported by epidemiological studies, but have these decreases in risk factors been the result of drug therapy? When drug therapy obtain this effect, has it been shown that it translates into improvements in morbidity or mortality for obese patients?

**There is no shortage of examples in which a reduction in a risk factor by a drug therapy was accompanied by a net increase in mortality.** For example, *dronedarone* reduces atrial fibrillation, which is a risk factor for stroke (5). Yet a

placebo-controlled trial was terminated early because of a two-fold increase in the incidence of stroke and a five-fold increase in all-cause mortality (1% versus 0.2% with placebo) were observed in participants treated with *dronedarone* (5). There is no question that *torcetrapib* has a positive effect on cholesterol, but its development was stopped after a placebo-controlled trial showed a higher mortality rate among the patients who received *torcetrapib* (6).

The EMA states in the draft guideline that “(...) *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*”. This statement shows that even the CHMP recognises that a decrease in certain risk factors is an unreliable endpoint, especially when extrapolating the results of clinical trials to routine practice. This is exactly why *Prescrire* insists that the efficacy of these drugs must be based on demonstration of a reduction in morbidity and mortality, rather than on modest weight loss alone.

**Efficacy endpoints: weight loss alone is not enough as a primary endpoint.**

Body weight is a useful marker in the follow-up of certain conditions such as hypercholesterolaemia and diabetes. But in the prevention of the complications of obesity it is only a surrogate marker. In particular, **the degree of weight loss that can be regarded as clinically meaningful is unknown**. Furthermore, if patients regain the lost weight after withdrawal of the medicinal product, as they frequently do, no tangible benefit will have been derived from the short-lived weight loss achieved.

As far as the prevention of the complications of obesity is concerned, **a weight loss of a few kilograms (e.g. a 5% reduction in body weight) is unacceptable as the primary endpoint**. The revision of the guideline on medicinal products used in weight control must add the **requirement for long-term follow-up of patients after discontinuation of the treatment** to evaluate whether or not the effects of the treatment are maintained (7).

To evaluate the prevention of the complications of obesity, the clinical documentation must necessarily include comparative trials in which **the**

**primary endpoint is the incidence of the complications of obesity, such as cardiovascular events** (morbidity). The mortality has to be a compulsory endpoint. The evaluation of morbidity and mortality requires clinical trials with **a statistical power sufficient to detect an increase of incidence of these endpoints, with a follow-up of at least 5 years** prior to submission of the MA application, followed by medium-term follow-up (a post-authorisation efficacy study) for at least an **additional 5 years**.

### **Study design: do not expose patients to unacceptable risks**

The section of the guideline that deals with study design meets the needs of patients and healthcare professionals on the whole, but *Prescrire* has three major comments to make (1):

**1.** All trials, regardless of their duration, must include a **run-in period** during which patients are treated with appropriate **lifestyle measures** (dietary changes, exercise, etc.). Patients for whom such measures appear sufficient should not be enrolled in the trial, to prevent unnecessary exposure to the adverse drug reactions of a novel drug whose harm-benefit balance is as yet unknown.

**2.** In addition, we maintain that a trial **duration** of at least 12 months is insufficient. In order to determine whether the effects of the treatment are maintained, it is essential to conduct clinical trials with a follow-up of at least **5 years prior to submission of the MA application**, followed by **medium-term surveillance (a post-authorisation efficacy study) for at least an additional 5 years**.

**3.** Finally, the draft guideline recommends **“actively-controlled”** trials. The final guideline must specify which active treatments are considered acceptable and which are unacceptable due to their unfavourable harm-benefit balance. The preferred treatments should be **non-pharmacological** (nutritional and/or

psychological/behavioural support, gastric banding or the use of another established medical device). For example, it would be unacceptable to include a group treated with an amphetamine anorectic, as these agents have been demonstrated to have an unfavourable harm-benefit balance in long-term use (3).

**Adverse effects: require thorough assessment before authorisation, in order to at least “do no harm”, followed by intensive surveillance**

The draft guideline states that trials should include thorough evaluation of the **neuropsychiatric adverse reactions** “*for all centrally acting agents*” and of **cardiovascular adverse reactions** (except “*in the absence of an increased cardiovascular risk in pre-clinical and clinical studies*”). These are welcome measures but must be **extended to include all medicinal products proposed for the treatment of obesity**, irrespective of their postulated mechanism of action.

**Evaluate the adverse effects of rapid weight loss, including increased fracture risk.** While there is evidence that obesity offers some protection against fractures and that bariatric surgery appears to reduce bone density, the draft guideline does not recommend evaluation of fracture risk (8). Yet it is reasonable to suspect that weight loss increases the risk of bone fractures.

**Also systematically evaluate the all other already known adverse effects of other weight-control drugs, e.g. renal and pancreatic failure.** The mechanisms through which drugs act are usually postulated, and rarely fully known. **Unexpected and sometimes paradoxical adverse effects are regularly reported** with drugs of many classes after their introduction on the market. For example, no-one suspected before their market introduction that certain “selective” serotonin reuptake inhibitor antidepressants would actually increase the risk of suicide in certain depressed patients (9). And gambling addiction was an equally unforeseen adverse effect of dopaminergic drugs used in patients with Parkinson’s disease (10).

To help manufacturers determine all the adverse effect variables that should be investigated in clinical trials, the revised guideline must include an **overview of the various mechanisms underlying the known adverse effects of weight-control drugs**, in particular anorectic agents.

The revised guideline should at least list the adverse effects of the weight-control medicines that are already marketed, and update it as new effects come to light: for example, **renal and pancreatic failure** are adverse effects of *orlistat* that were not recorded in its original MA dossier in 1997 and should now be looked for systematically in clinical trials of all weight-control medicines (7).

In addition, the revised guideline on medicinal products used in weight control should stress the need to prohibit simultaneous use of synonyms when coding adverse effects, which spreads adverse effects across different categories, thereby reducing the reported incidence of the adverse effect of interest (a). Better still, the revised guideline should **suggest how to code adverse effects, to minimise the risk of signals being diluted**, particularly for adverse effects that in practice can be coded in different ways.

**Risk assessments on interactions and addiction are also needed.** The revised guideline on medicinal products used in weight control must also demand, for all of these agents, and not just for amphetamine anorectics, a **risk assessment on:**

- **interactions** between the investigational product and medicines commonly used by obese patients (antidiabetics, antidepressants, etc.);
- **addiction** to weight-control medicines through either their inherent addictiveness, possibly associated with a withdrawal syndrome, or their effect on weight loss, given that they are bound to be used by high-risk patients, for example those with eating disorders.

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a- For example, the increased risk of suicide in children taking SSRI antidepressants (*paroxetine*: Seroxat®, Deroxat®) was long concealed because it was coded as either "hospitalisation" or "emotional lability" etc.

## To conclude: lessons have to be learnt from past public health disasters caused by anorectic agents

The revised guideline must take on board the lessons learnt from past public health disasters caused by anorectic agents (11): enhanced surveillance of the adverse effects of weight-control medicines is necessary for at least 5 years post-authorisation. But these post-authorisation “safety” studies must not be used as a pretext for approving dangerous, under-evaluated medicines, nor to keep dangerous medicines on the market pending the results of this study, as happened with *sibutramine* and *rimonabant* (b).

When an adverse effect is suspected, especially involving a weight-control medicine that has not been shown to reduce morbidity and mortality, the **priority must always be given to patients’ protection.**

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### Selected references from Prescrire’s literature search.

- 1- Committee for Medicinal Products for Human Use (CHMP) “Guideline on clinical evaluation of medicinal products used in weight control - Draft for public consultation” London, 26 June 2014 (ref. EMA/CHMP/311805/2014): 11 pages. Deadline for comments: 31 January 2015 (cvswpsecretariat@ema.europa.eu)
- 2- European Medicines Agency - Committee for Medicinal Products for Human Use “Concept paper on the need for revision of the guideline of medical products used in weight control” London, 20 September 2012 (ref. EMA/CHMP/229823/2012): 3 pages.
- 3- Prescrire Editorial Staff “Response to EMA public consultation. Medicinal products used in weight control: first, do no harm” Paris. english.prescrire.org 31 December 2012: 4 pages.
- 4- European Medicines Agency - Committee for Medicinal Products for Human Use “Guideline on clinical evaluation of medicinal products used in weight control” London, 15 November 2007

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**b-** For example:

– *sibutramine* (formerly marketed as Sibutrol<sup>®</sup>) is an anorectic that was withdrawn from the European market in 2012, mainly because it increased the risk of myocardial infarction and stroke. It took 9 years and the results of a post-authorisation outcome study including 10 000 patients that began in 2002, for this decision to be finally taken (ref. 12).

– In 2008, after several months of prevarication following the damning results of post-authorisation studies (adding new contraindications, then new special warnings and surveillance measures), the EMA finally withdrew *rimonabant* (formerly marketed as Acomplia<sup>®</sup>) from the European market, having acknowledged its unfavourable harm-benefit balance in the treatment of obese or overweight patients with associated risk factors, mainly because it increased the risk of suicide (refs. 13,14).



(Doc. Ref. CPMP/EWP/281/96 Rev.1): 9 pages.

**5-** Prescrire Rédaction "Dronédarone: un essai arrêté pour excès de mortalité" *Rev Prescrire* 2011; **11** (336): 747.

**6-** Prescrire Rédaction "Torcetrapib: arrêt du développement d'un hyperlipidémiant" *Rev Prescrire* 2007; **27** (280): 108.

**7-** Prescrire Editorial Staff "Orlistat – no hurry..." *Prescrire Int* 1999; **8** (42): 99-104.

**8-** Stein EM and Silverberg SJ "Bone loss after bariatric surgery: causes, consequences, and management" *The Lancet Diabetes & Endocrinology* 2014; **2** (2): 165-174.

**9-** Prescrire Editorial Staff "Antidepressants: suicide among young adults" *Prescrire Int* 2008; **17** (93): 23.

**10-** Prescrire Editorial Staff "Hypersexuality due to dopaminergic drugs" *Prescrire Int* 2005; **14** (80): 224.

**11-** Prescrire Editorial Staff "The amphetamine appetite suppressant saga" *Prescrire Int* 2004; **13** (69): 26-29.

**12-** Prescrire Editorial Staff "Sibutramine: cardiovascular events" *Prescrire Int* 2010; **19** (107): 125.

**13-** Prescrire Editorial Staff "Rimonabant: suicides and depression" *Prescrire Int* 2007; **16** (92): 250-251.

**14-** Prescrire Editorial Staff "Rimonabant: obesity: loss of a few kilos, many questions" *Prescrire Int* 2006; **15** (84): 123-126.