

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

- In its response to the European Medicines Agency's consultation on the revision of the guideline on medicinal products used in weight control (1), *Prescrire* would like to remind the EMA of the importance of the principle: "first, do no harm". A weight loss of a few kilograms achieved through drug therapy cannot in itself justify exposing obese or simply overweight patients to a disproportionate risk of adverse drug reactions, especially since the lost weight is very often regained within months of discontinuing the treatment.
- Taking on board the lessons learnt from past public health disasters notably due to drugs with appetite suppressant effects, such as *sibutramine* (Sibutral^o) and *benfluorex* (Mediator^o), and to *rimonabant* (Acomplia^o), *Prescrire* urges the European Medicines Agency to impose stricter requirements so that weight-control medicines that do more harm than good can no longer be authorised in Europe.

Prescrire supports the European Medicines Agency's (EMA) initiative to revise the guideline on medicinal products used in weight control (1,2).

The original guideline adopted in 2007 by the EMA's Committee for Medicinal Products for Human Use (CHMP) has proved insufficient to protect Europe's obese and simply overweight patients from the adverse effects of a number of medicinal products that have since been withdrawn from the market because they were doing more harm than good (a)(2).

Many weight-control medicines are currently being developed, and some are at a very advanced stage, such as the worrying *phentermine + topiramate* combination and certain amphetamine-like drugs (b,c).

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.

Medicinal products used in weight control: of limited use in the treatment of obesity, and a risk of abuse. Obesity is increasingly prevalent in wealthy countries, sometimes associated with eating disorders, and is a cause of morbimortality (3,4). To prevent the complications of obesity and in particular its cardiovascular risks, measures to encourage weight loss in obese patients should focus on a balanced, moderately low-calorie diet, regular moderate exercise, and individualised mainly psychological support (4).

Furthermore, weight-control medicines are frequently prescribed in everyday practice for patients who are simply overweight, sometimes off-label, often in an attempt to help patients who are unhappy about their physical appearance. The number of people exposed to the risks of the adverse effects of these medicines far exceeds the number of obese patients. For example, *benfluorex* (Mediator[®]) was extensively prescribed and taken off-label as an appetite suppressant for over 30 years until its withdrawal from the French and European market in 2009; it has been estimated to have caused hundreds of deaths in France and thousands of cases of valvular heart disease of varying severity (5).

When assessing an MA application for a medicinal product for use in weight control, regulatory agencies must also take into account their inevitable abuse as non-essential dieting aids. This widespread use of appetite suppressants means that they should only be approved if there is hard evidence that they have no serious adverse effects, particularly during prolonged use.

Evaluation of efficacy: demand evidence of a reduction in morbidity and mortality. 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, and a correlation with clinical outcomes has not been clearly established. In particular, the degree of weight loss that can be regarded as clinically relevant is unknown. Furthermore, if patients regain the lost weight after withdrawal of the medicinal product, no tangible clinical benefit will have been derived from the short-lived weight loss achieved.

As far as preventing the complications of obesity is concerned, a weight loss of a few kilograms (e.g. a 5% reduction in body weight) is unacceptable as a primary endpoint. The revision of the guideline on medicinal products used in weight control (section 3.6 “Strategy and design of clinical studies”) 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** (4).

To evaluate the prevention of the complications of obesity, the **clinical documentation must necessarily include comparative trials in which the primary endpoint is mortality and a reduction in the incidence or severity of the complications of obesity, such as cardiovascular events.** This evaluation of morbidity and mortality requires **clinical trials 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.**

Regarding the choice of comparators, it is important to stress that weight-loss medicines can only be used as an adjunct to dietary and lifestyle measures. Without dietary and lifestyle measures, patients often regain the lost kilos within weeks or months of discontinuing drug therapy, abolishing any tangible clinical benefit (4). **The revision of the guideline on medicinal products used in weight control (section 3.6 “Strategy and design of clinical studies”) must specify the most pertinent comparators for evaluating new weight-control medicines:** evaluation versus non-pharmacological measures (either a combination of a balanced, moderately low-calorie diet, regular moderate exercise, and individualised support; or gastric banding or another well-established medical device) or versus another medicinal product that has already been demonstrated to reduce morbidity and mortality with a favourable harm-benefit balance, or versus combinations of these treatments.

Evaluation of adverse effects: demand thorough assessment before authorisation in order to at least “do no harm”, then intensive surveillance. The **adverse effects of weight-control medicines must be looked for proactively in clinical trials.** The guideline on medicinal products used in weight control (section 3.7 “Safety aspects”) must of course be revised to add the need to **look for cardiovascular** (by echocardiography, etc.) **and neuropsychiatric adverse effects** (in particular suicidal ideation, suicide and depression), especially when the drug in question has appetite suppressant properties. If this had been done for *rimonabant* (Acomplia[®]), the associated suicide risk would have been detected sooner (6).

However, a more comprehensive search for all of the medicine's adverse effects is necessary. 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 appetite suppressants, as well as the adverse effects of rapid weight loss.**

The revision of the 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).

The revision of the 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 (d). Better still, the revision of the guideline on medicinal products used in weight control should suggest how to code adverse effects to minimise this risk of dilution, particularly for adverse effects that in practice can be coded in different ways.

The revision of the guideline on medicinal products used in weight control must also **demand risk assessments on:**

- **interactions between the tested weight-control medicine 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.

In addition, the revision of the guideline must take on board the lessons learnt from past public health disasters caused by appetite suppressants (8): **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 to approve dangerous, under-evaluated medicines, nor to keep dangerous medicines on the market pending the results of the study, as happened with *sibutramine* and *rimonabant* (a). When an adverse effect is suspected, especially involving a weight-control medicine that has not been shown to reduce morbidity and mortality, the benefit of the doubt must always be given to patients, and necessary timely measures to safeguard public health must be taken.

Prescrire urges the EMA to impose stricter requirements so that the new guideline represents a tangible improvement over the one adopted in 2007.

It is time, at the end of 2012, to learn from past drug disasters caused by appetite suppressants, including *sibutramine* (Sibutral°, now withdrawn) and *benfluorex* (Mediator°, now withdrawn), and by *rimonabant* (Acomplia°, now withdrawn), and to stop exposing European patients to the adverse effects of weight-control medicines that do more harm than good.

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Notes:

a- For example:

- *sibutramine* (formerly marketed as Sibutrol[®]) is an appetite suppressant that was withdrawn from the European market in 2010, 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. 9);

- 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[®]) 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. 6,10).

As of late 2012, *orlistat* (Xenical[®], Alli[®]) is still marketed in Europe, yet its adverse effect profile is a continuing cause for concern with a growing list of changes to its MA (variations): addition of serious adverse effects (hepatitis, pancreatitis, oxalate nephropathy), warnings about interactions with other drugs. Another risk factor is that *orlistat* is available for self-medication without a prescription in the European Union (refs. 4,7).

b- The US Food and Drug Administration (FDA) refused to license the *phentermine + topiramate* combination in July 2011, before approving it one year later, in July 2012, on the recommendation of an advisory committee. In Europe, the CHMP issued a negative opinion on this combination in October 2012, concluding that its benefits did not outweigh the risks of its long list of adverse reactions (ref. 11). The company announced its intention to appeal against this decision, as is often done in the hope that the CHMP will revise its opinion from negative to positive. The CHMP's verdict is due in the first quarter of 2013.

c- Obesity represents a major commercial opportunity for pharmaceutical companies: according to some analysts, a medicinal product used by 1% of obese patients would generate sales of over \$1 billion (ref. 3).

As of late 2012, a number of different projects are at varying stages of advancement, for example:

- the psychotropic drug *lorcaserin* was licensed in the US in 2012, after an initial rejection in 2010; it is currently being evaluated by the EMA;

- an application for the *bupropion (amfebutamone) + naltrexone* combination is due to be submitted to the FDA in 2013; the company decided not to apply for an MA for the *bupropion (alias amfebutamone) + zonisamide* combination (Empatic[®]);

- *lisdexamfetamine* is currently undergoing phase III clinical trials in binge eating disorder (ref. 3);

- the antidiabetic drug *liraglutide* (Victoza[®]) is under development for obesity;

- not to mention the medicines used off-label in obesity, such as the antidiabetic drugs *exenatide* (Byetta[®]) and *benfluorex*.

d- 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.

References:

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