23 June 2016
EMA/414592/2016
Committee for Medicinal Products for Human Use (CHMP)

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

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	European Association for the Study of Diabetes (EASD)
2	European Association for the Study of Obesity (EASO)
3	EFPIA
4	Prescrire

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1. General comments – overview

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2	The European Association for the Study of Obesity (EASO) welcomes the fact that the European Medicines Agency (EMA) has taken the initiative to review and update its 'guideline on clinical evaluation of medical products used in weight control'. It is widely acknowledged that obesity is the gateway to many other disease areas, including most NCDs, and that weight management will play a major role in reducing morbidity and mortality of populations in Europe and world-wide. EASO therefore supports the development of these updated guidelines, and the content therein. EASO suggests that the EMA might consider the following amendments: 1) In the introduction to the guidelines obesity is described as a 'chronic clinical condition'. EASO suggests that obesity should rather be referred to as 'a disease state that in some circumstances can develop into complications'. It is worth noting that obesity was introduced in the International Classification of Diseases (ICD) back in the 1950s and can be currently found in ICD10 under the chapter of "Endocrine, nutritional and metabolic diseases". 2) It is widely recognised that the measurement of body composition and the impact on body fat itself, is an important tool when assessing patients, especially when dealing with visceral adiposity. EASO suggests that improvements in waist circumference and/or body composition, as opposed to weight loss alone, could be used as alternative, more realistic, indicators for success. Thus, where validated equipment is available, body composition should be added to the standard portfolio of measurements. 3) It should be noted that the management of co-morbidities and improving quality of life (QoL) and well-being of obese patients	1)Accepted 2) Weight loss is considered as the most relevant endpoint from a regulatory point of view as it is associated with clinically relevant beneficial effects. The clinical relevance of the magnitude of improvements in waist circumference and/or body composition is still less well established. These outcomes are therefore only recommended as key secondary efficacy endpoints in the current guideline. 3) Accepted

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	should be included in treatment aims. QoL should be assessed with validated questionnaires.	
3	This new draft guideline is very welcomed, and EFPIA appreciates the opportunity to comment on this draft guideline. EFPIA welcomes the linking of the need for positive CV outcome data to claims rather than approval for marketing. About the title and terminology used in the guideline: “used in weight control” diminishes the medical importance of obesity. EFPIA propose a change of the title and terminology used throughout the document, preferably to: “used in treatment of obesity” . Because the development of treatment of obesity is global, EFPIA finds it important that the requirement described in this guideline is aligned with other global requirements, i.e. the USA, FDA, and that the treatment guidelines and definitions issued by international physicians associations are accepted by the Agency.	Not accepted. With respect to terminology, the products are not only used to treat obesity but also overweight. Therefore, weight control is considered as adequate.
4	**In its response to the EMA consultation, *Prescrire* 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.** 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). The current consultation follows a previous consultation organised by the EMA in late 2012 on the need for revision of the	

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	existing guideline, to which *Prescrire* responded (2,3). *Prescrire* 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. *Prescrire* 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 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°) 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.	

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	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	Not accepted. There is scientific support that weight loss has a positive effect on CV risk factors, as well as other weight related comorbidities. There is also a lot of evidence to support that a beneficial effect on such risk factors indeed reduces morbidity and mortality in the long term. A direct demonstration of a reduction of mortality/morbidity is therefore not considered as an absolute requirement for approval of a weight reducing agent. Indeed such a study would be of considerable length and would delay access of the medicines to patients which is not considered as adequate considering that the surrogate markers of efficacy (i.e. CV risk factors including loss of body weight) are considered as reliable. Weight loss is also associated with other benefits which is reflected in the guideline *("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)")* Partly accepted. There is no reason to believe that weight loss as a result of drug therapy would not have a similar beneficial effect on morbidity and mortality compared to weight loss due to life style interventions. However, the safety profile of the drug must be carefully evaluated to ensure that the benefits indeed outweigh any risks. The safety section of the guideline has been reinforced compared to the previous version, and with regard to the requirements for the evaluation and quantification of the cardiovascular

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	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**	risk at the time of licensing the GL further refers to the CHMP's "Reflection paper on assessment of cardiovascular safety profile of medicinal products".

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	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	1) Partly accepted. There is no absolute requirement for a run in period. However, it is clearly stated that *"Pharmacological options are not recommended until at least one trial of an appropriate weight-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"*. and *"Eligible patients are those for whom at least one trial of an appropriate weight-reducing diet has proven to be insufficient".* 2) Partly accepted. To assess effect on weight management, 12 months duration is considered as adequate. However, the guideline also states that *"To document the effect on some weight related outcomes (e.g. delay in onset/prevention of type 2 diabetes), longer study durations may be needed ".* Also for safety reasons, longer durations may be

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	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	requested pre or post approval. 3) Partly accepted. Studies should be placebo controlled, but products approved in the EU may also be included in the studies; *"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".* Partly accepted. As for all medicinal products, all reported adverse events will be assessed irrespective of mechanism of action. The adverse reactions specifically mentioned in the guideline (including a section on abuse potential) are those that require extra attention from sponsors. With respect to CV safety, references are made to the CHMP's "Reflection paper on assessment of cardiovascular safety profile of medicinal products". With respect to interactions, reference is made to relevant PK guidelines.

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	fractures. **<u>Also systematically evaluate the all other already known adverse effects of other weight-control drugs, e.g. renal and pancreatic failure.</u>** 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	

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	adverse effects across different categories, thereby reducing the reported incidence of the adverse effect of interest ([1]). 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. **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	

[1]- 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.

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	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* ([2]). 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**	

[2]- For example:
– *sibutramine* (formerly marketed as Sibutral°) 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°) 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).

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
65-70	1	Obesity is defined and it is stated that "**severe obesity is defined as BMI > 40 kg/m^2**" I think this is not correct; severe obesity is defined as BMI> 35 kg/^{m2}, and morbid obesity BMI> 40 kg/m^2 (and ultra obesity BMI > 50 kg/m^2)	Accepted.
312-314	1	Comments: Some drugs may have unfavourable effects on cardiovascular risk factors – for example increase LDL. In my view, a drug with a profile of an adverse, unfavourable effect on any cardiovascular risk factor would qualify for the obligation to perform a cardiovascular outcome study –*independent of results of a meta-analysis of cardiovascular endpoint observed in the study programme.* In the current wording, CV outcome studies are only warranted if such a meta analysis provides a signal. The second reason for an outcome study (line 312-314) suggests it, but probably does not include it totally. Example: suppose a drug does not have an intrinsic safety concern from the molecule / mechanism of action, but it shows a slight increase in LDL. Nevertheless, the meta analysis of CV outcomes does not provide a signal (RR 0,75, with CI upper bound	Accepted. This issue is covered in more detail in the "Reflection paper on assessment of cardiovascular safety profile of medicinal products".

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		1,28 may not be obliged to perform a CV safety trial, but I suggest that it should. I could be arranged by adding a few lines under 4.3 (157-161) and to point two lines 312-314.	
Lines 84-85	2	Comments: Regarding ” Relevant decreases in certain risk factors associated with obesity have been seen with loss of at least 5 to 10% of initial weight. Comment: According to the AHA/ACC/TOS Guidelines for the management of overweight and obesity in adults (Obesity. 2014;22(S2):S41-S410), it is stated that a sustained weight loss of 3 to 5% produce clinically meaningful health benefits. This may be implemented in the introduction of this EMA document as well.	Accepted.
Line 146-147	2	Comments:…..where response is equal to or more than 10% weight loss at the end of a 12-month period. (change from more than 10%)	Accepted.
Line 157	2	Comments: A new weight-lowering agent should in general show a neutral or beneficial effect on parameters associated with cardiovascular risk (e.g. blood glucose, blood pressure, lipid levels). ADD "heart rate" to these parameters.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 171-175	2	Comments: Quality of life should be assessed with validated questionnaires	Accepted.
Lines 214-215	2	Comments: Regarding "For studies with duration of 12 months or longer, this may not be necessary. For studies with ≤ 12 month duration,..." As this statement stands, studies of 12 months duration (which is a typical duration) could be included in either statement. It would be best to state that for studies of < 12 month duration (instead of ≤ 12 month duration).	Accepted.
Lines 215-216	2	Comments: For studies with ≤ 12 month duration, a run-in period in which all patients should be given similar instructions, advice and encouragement with regard to diet and behaviour modification and exercise should be implemented before randomisation. Comment: How long before randomization? Many patients have only a certain potential of weight reduction, and much of it may be "used up" in the prerandomization phase. A suggestion could be to implement these instructions for two weeks before randomization. It should also be acceptable to remove the run-in period entirely for these studies.	Partly accepted. The issue of run-in period will be further considered.
Lines 62-63; 91-93;	3	"... Another aim of weight reduction is to reduce the prevalence and severity of other, non-cardiovascular related complications such as sleep apnoea, joint pain,	Not accepted. There is no intention to cover all complications of obesity in the guideline, but rather to focus on such that in

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171-173		urinary incontinence, impaired fertility, depression, anxiety and functional limitations, such as decreased mobility..." Comment: To include effects on outcomes other than those relating to the cardiovascular system is welcomed. EFPIA also suggest to include non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) in the relevant paragraphs given their association with obesity	particular affects the quality of life.
65-74	3	The BMI criteria are based on population studies and reflect average body composition. Differences in different ethnic populations are recognised, but a caution should be added for individuals who are not of typical body composition (eg, highly muscular, etc.).	Accepted.
71-74	3	Proposed change: To align with lines 91-93, the following additional text is suggested after the sentence with reference to Hamer et al.: *Obesity causes an increase in all-cause mortality and reduced life expectancy, and several non-cardiovascular significant complications such as cancer, diabetes type 2, pre-diabetes, mechanical /functional disabilities, impaired mental health and Quality of Life.*	Not accepted. This is already mentioned in the beginning of the introduction.
103 - 109	3	Comment: The restriction to only list the three proposed categories of pharmacological treatment is a concern. Knowing that there are already drugs being studied with numerous other mechanisms, this guideline may become quickly outdated. Other examples currently include: (1) PYY3-36 (natural gut hormone peptide	Accepted.

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		YY3-36), (2) AOD9604 (synthesized portion of HGH), (3) *velneperit* (neuropeptide Y5 antagonist), (4) NGD-4715 (melanin concentrating hormone receptor-1 (MCH-1) antagonist), (5) CYT009-GhrQb (anti-ghrelin vaccine); GI181771X (CCK-A agonist), (6) *beloranib* (methionine aminopeptidase 2 (MetAP@) inhibitor); EFPIA propose not to restrict the guideline to only the 3 proposed pharmacological treatment options. It is suggested to keep the listing open, explaining that these are examples, and not limited to the listed pharmacological options. A further proposal is provided with the next comment. Comment: The three categories of pharmacological options listed are not comprehensive. EFPIA suggest the following changes to more accurately capture the mechanism of action and guide the drug development. Another rationale for broadening the scope of the drug class definitions is that new drug classes are in development, which will easier fit into the new proposed class definition described by primary mode of action. Proposed changes: In principle, pharmacological options include, the following *mechanisms of action*: – ~~Centrally acting anorectic agents~~ *Drugs that regulate appetite* ~~acting~~ via catecholamine and/ or serotonin*, or other central or peripheral* pathways*, such as GLP-1 receptor agonists*. These drugs are associated with reduced subjective hunger ratings and reduced food intake.	

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		– Drugs that inhibit the absorption of nutrients, promoting weight loss without having a specific effect on appetite*, such as orlistat*. – Drugs that modulate ~~incretin receptor activity, such as GLP-1 (glucagon-like protein-1) receptor agonists which act primarily via a reduction in food intake~~*energy expenditure and promote weight loss via effects on metabolic rate, such as sympathomimetics*~~.~~	
104 (and other places)	3	… ~~anorectic~~ anorexigenic agent	Accepted.
112-113 and Section 5: 180-182	3	The general goals, scope and target population are defined in slightly different ways throughout the document. Goals stated in the introduction (lines 81-82: reduce body weight and maintain lower body weight, and lines 91-92: reduce the prevalence and severity of other, non-CV related complications) do not align with the selection of patients listed in section 5 (lines 178-179: patients eligible for pharmaceutical therapy should have a degree of obesity associated with a significant health risk, and lines 180-182: obesity should be diagnosed on the basis of BMI ≥30…For patients with multiple CV risk factors, a lower BMI could be considered), nor the Scope in section 2 (lines 112-113: scope of this guideline is restricted to the development of pharmacological options for the treatment of obesity.) Proposed change: EFPIA propose to broaden the statement of the scope of the guideline to also include overweight patients with BMI ≥27 and associated risk factors and complications, not only restricted to CV-risk factors but also including the non-cardiovascular related complications already listed in lines 92-93. This will thereby address the aim to reduce the	Accepted.

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		prevalence and severity of the 'feeling and function' of obesity related risk factors and complications and reduced quality of life, and will also harmonise with the draft FDA guidance (Feb 2007). Proposed change: New text in lines 112-113: **".. restricted to the development of pharmacological options for treatment of *patients with obesity and overweight patients with associated weight-related comorbidities and its complications*."** New text for lines 181-182: For patients with ~~multiple CV~~ *a weight related* risk factor~~s~~ *or comorbidity,* a lower BMI at baseline *(e.g. ≥27 kg/m^2)* could be considered.	
137	3	Proposed text change to align with the stated general goals (lines 81-82):: Reduction of body weight *or maintenance of a lower body weight* should be the primary efficacy endpoint in the clinical studies…	Not Accepted. For recently approved products, the wording of the indication has been ; *X is indicated, as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients,* i.e. no mentioning of maintenance of effect. Therefore, the guidance will focus on management and not maintenance.
140-155	3	These endpoints are not the same as those recognized by USA,FDA. -Proposed change (if any): EFPIA recommends a harmonisation of guidance and endpoints between the FDA and the EMA and according to international clinical treatment guidelines.	Not accepted. The requirements are not that dissimilar; EU 5-10 % vs FDA 5%.
Section 4 Efficacy criteria and methods to assess efficacy	3	Comment and proposed change: Suggest to change the text into bullets (as below) in order to increase clarity and understanding. Also suggest slight change of responder text to align the primary and secondary endpoints. *Two different approaches to primary efficacy analyses*	Accepted.

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4.2 Reduction of body weight… Line 141 to 148		*are described:* • Percentage weight loss relative to baseline, *and compared to placebo.* Demonstration of a clinically significant degree of weight loss of at least 5-10% of baseline body weight, which is also at least 5% greater than that associated with placebo • Proportions of responders *Primary: Proportion of subjects achieving* a response of *greater than or equal to* 10% weight loss *from baseline* at the end of 12 months. Secondary: *Proportion of subjects achieving* a response of greater than or equal to 5% weight loss *from* baseline at the end of 12 months	
Line 149-150	3	Comment: It is important to take into account that the predictive value at 3 months (alternative 12 weeks) should be assessed on target treatment dose rather than including any titration to target dose. This efficacy analysis, based upon stopping criteria in the label, should be relevant to include in the SmPC. Further guidance regarding whether an analysis of both efficacy and safety for the responder population should be performed for inclusion in the SmPC.	Partly accepted. In this section of the guideline, the stopping rule is referring to efficacy evaluation.
156-167; 297-298	3	Cardiovascular risk – section 4.3; 4.4 and 7.4.1: Section 7.4.1 sets out two approaches to *exclude* an increased cardiovascular risk – a meta-analytic approach and an outcome study. The outcome study would not be much different in scope than one that would demonstrate benefit per sections 4.3 and 4.4. Given the low event rate in an obese population this could be challenging.	Not accepted. For further details reference is made in the text to the CHMP's "Reflection paper on assessment of cardiovascular safety profile of medicinal products".

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		Given the above, it would be helpful if the guideline could be more specific in terms of what is acceptable re: characterising risk: - Proposed change: For a program with no detectable risk, i.e. no signal seen in non-clinical and earlier phase clinical studies and if unlikely to arise from the mechanism of action: • No formal powered meta-analysis or outcomes study is required. Events should be collected and adjudicated and included in the risk-benefit analysis with other events For a program with an identified risk: A powered meta-analysis or outcomes study should be undertaken in order to rule out a pre-specified level of risk	
158-161	3	The draft guidance states that for specific claims with respect to beneficial effects on cardiovascular endpoints other than body weight, relevant guidelines should be followed. It is not clear whether this refers to the method for the evaluation of the relevant endpoints, or for the efficacy thresholds, or otherwise. There are no guidelines relevant to the impact on the risk of the development of diabetes as an important secondary endpoint, so guidance related to this claim is suggested to be inserted in this document. The guidance should preferably discuss the beneficial effects of the treatment including those associated with weight loss and maintenance for a label claim.	Not accepted. The reference so other guidelines refers to the situation when a weight lowering product claims an additional indication, e.g. treatment of type 2 diabetes, lowering of serum lipids. This has been clarified in the text.

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165-167	3	Please further clarify “real world” sample of patients with obesity in reference to CV claims. *Examples of type and design of trials is appreciated.*	Accepted.
170-175	3	Section 4.5 describes co-morbidities related to overweight/obesity. Given its “high importance” it would be expected to be relevant for inclusion in the label (even if no such indication claim pursued) - would such assessment need to be included as secondary endpoints, rather than exploratory, using validated endpoints/symptom scores in order to support inclusion in labelling (SmPC section 5.1)? In order to support as part of indication claim it is noted to follow respective guidelines, but guidance on how to incorporate this in same development program would be helpful. Proposed change (if any): Assessment of the effect on comorbidities secondary to overweight/obesity such as sleep apnoea episodes, joint pain, urinary incontinence, impaired fertility, depression, anxiety and functional limitations, such as decreased mobility, is of high importance, and should therefore be considered, ~~considering~~ given that these comorbidities may severely impact quality of life. Relevant and validated end points and symptom scores *should be considered to be used in order* to assess beneficial effects of the study drug on these co-morbidities *in order to support inclusion in the label either as part of indication statement or under Section 5.1. These end points and scores need not to be used if no beneficial effects on co-morbidities are to be claimed, included in the label, or used as part of the benefit-to-risk assessment*.	Partly accepted. The inclusion of such results in section 5.1 would depend on the clinical relevance of the results. This is a general “rule” for all therapeutic areas, and there is no need to specify it in this particular guideline. For inclusion in the indication, see previous comment.
Line 178-	3	Further clarity regarding “significant health risk” for patients eligible for pharmaceutical therapy is requested.	Partly accepted. Sentence deleted since it is unclear.

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179		Rationale: Do patients with obesity and a positive family history have “significant health risk” (e.g. as primary prevention of CV disease or diabetes) or does significant health risk mean obesity and already present dyslipidaemia or dysglycaemia, etc.? Is pharmaceutical therapy for obesity indicated as primary prevention of obesity related complications, or is it intended as secondary prevention after obesity related complications have already developed?	
183-186	3	Is it intended that epidemiology or prevalence data *should be presented* to define ‘a representative sample for the Class II and III obesity’?.	Partly accepted. Has been clarified
Lines 214-219	3	The purpose of the run-in period is not clear and further guidance is warranted to clarify the aim of the run-in period. Including a run-in period will likely improve secondary endpoints, and thereby minimise the efficacy demonstrated on secondary endpoints with the pharmaceutical therapy, hence this should be taken into consideration in the evaluation of efficacy and in pooling data from such a study with remaining studies. The requirement for a lifestyle intervention run-in period has not been required for approval of other drugs, e.g. hypertension or dyslipidaemia, so it is not clear why it would be a requirement in the case of obesity.	Partly accepted. Propose to delete the need for diet run-in
214-221	3	There is no need for a diet run-in in a study of any duration. Prior studies have demonstrated similar efficacy (compared with control) regardless whether a run-in was included or not, and regardless of the intensity of the non-pharmacologic intervention	Partly accepted. Propose to delete the need for diet run-in

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		provided to all participants (from no intervention to a very-low calorie diet). Establishing treatment effect in short studies is not dependent on a run-in nor on the kind of diet or other lifestyle intervention applied. Trial designs should be best suited to the objectives of the trial and the phase of development.	
219-221	3	It is suggested to modify the text about the effect of other drugs on body weight to include broader examples of other drug classes known to impact body weight and frequently used as concomitant treatment in patients with obesity *(anti-diabetes medications, psychoactive agents, steroids, beta-blockers, etc.).* It is not clear how such an effect "should be taken into account."	Accepted.
222-228	3	It is confusing if the primary end point assessment could/should be based on 6 or 12 months?	Accepted.
225 and 227	3	To align with the general goals listed in lines 81-82, it is suggested to incorporate weight loss maintenance into this section. Proposed change: Line 225 "weight development" into "*weight loss maintenance*" Line 227 "weight development" into "*weight loss maintenance and weight regain*"	See previous comments. The guidance focuses on weight management instead of loss and maintenance
Lines 226-228	3	Is the purpose of the withdrawal trial, as stated, to support the duration of the weight lowering effect (although no such criterion is used for other drug treatments for a chronic disease/condition), or is it to evaluate withdrawal or rebound effects? If the former, rationale is requested for why this requirement in this disease/condition. If the latter, the guidance should specify that this is	Accepted

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		only required for drugs with anticipated withdrawal symptoms based upon mechanistic or non-clinical studies. Thus further guidance is warranted to clarify the purpose and basis for calculation of the duration of the withdrawal trial.	
229-230	3	The possibility of different dose regimes, such as continuous or intermittent treatment should be considered.	Not understood, the sentence is included.
231-233	3	Certainly, any CNS-acting drug should have follow-up sufficient to assess CNS effects of withdrawal. However, follow up to asses effects of drug cessation on food intake and weight is prohibitively long and pointless, and guidance is lacking for how to calculate the duration of follow-up (based on product specific PK or otherwise). Obesity is a chronic disease, and like any chronic disease such as diabetes or hypertension or dyslipidemia, stopping treatment will result in patients returning to their pre-treatment condition. In obesity, just as it takes 6-12 months to achieve maximum efficacy, it will also take approximately 12 months to fully assess the effects of cessation of treatment on body weight.	Partly accepted. Is discussed.
237-240	3	"...Patients who fail to respond to treatment should be identified, as successful weight loss in the first months of treatment may predict long term effects... The predictive value of a range of % weight loss after e.g. 3 months treatment with respect to long term weight loss (e.g. after 12 months treatment) should be presented..." Comment:	Not accepted. Will depend on mechanism of action and must be optimized for each product.

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		The focus on the predictive value of weight loss at early time points is interesting. It would be helpful if the guideline could consider how early a "responder" population could be identified with different mechanisms	
255	3	The paragraph regarding the paediatric addendum is "lost" under the "Older patients" sub-heading. Proposed change (if any): Add sub-heading "Paediatric patients" before last paragraph regarding the paediatric addendum	Accepted.
Lines 261-263 and 268	3	The sentence "Non-clinical data in relevant animal models evaluating the potential effect of the test drug on different safety aspects should be conducted and provided as an instrumental element of the safety evaluation as outlined in ICH guidelines (e.g. S7A and S7B)" could be deleted and "safety pharmacology" could be added in line 268: "…secondary pharmacology, *safety pharmacology,* as well as key toxicological findings from non-clinical studies."	Accepted.
275-282	3	Agree with the general rationale to conduct prospective neuropsychiatric assessments based on relevant mechanism of action. Please clarify whether the requirement is only relevant for drugs acting via the catecholamines and serotonin pathways? Proposed new text: *"If there are any indications of neuropsychiatric safety issues from mechanistic, non-clinical, early clinical or marketed data, then* prospective assessment *of psychiatric, neurostimulant or cognitive adverse events such as* …should be included *with the best tools currently available."*	Partly accepted. Text amended in line with the suggested text, but more specific guidance concerning the preferred scoring tools/scales to assess neuropsychiatric side effects is considered to be outside the scope of this guideline.

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		Well-validated scoring tools do not exist for all of the potential adverse events noted. Will EMA provide more guidance regarding acceptable relevant and validated tools and how the potential adverse events noted can be scored and assessed? Will it suffice to capture and specifically analyse SMQ terms/Adverse Events for these terms, especially where no well-validated tools are available? If not, more guidance is requested.	
Line 286	3	Proposed change or additional text at beginning of section: *"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 included with the best tools currently available."*	Accepted.
295-337	3	Concern with adverse effects on CV disease is based on experience with centrally-acting anorexigenic drugs, such as sibutramine, all of which increase sympathetic outflow and increase heart rate and blood pressure to some, albeit very small, extent. The evaluation of CV risk should be based on the actual effects of the actual drugs being studied. Drugs with no adverse effects on CV risk factors, and certainly those with small beneficial effects on risk factors, should not be required to discharge a risk which has no basis in reality.	Partly accepted. As mentioned above, the requirements for the evaluation/quantification of the CV safety profile of drugs intended for weight management is addressed CHMP's "Reflection paper on assessment of cardiovascular safety profile of medicinal products". This section has been updated in line with this paper.
334-335	3	"... assessed in terms of internal and external validity and in relation to the overall risk-benefit ratio of the drug..." Comment:	Partly accepted. This section has been updated in line with CHMP's "Reflection paper on assessment of cardiovascular safety profile of medicinal products"

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		The acceptable benefit risk for a short-term indication, like “prior to surgery”, would be presumed to be different than chronic therapy. It would be helpful to provide clarity on this in the guideline	
345-346	3	Pulmonary arterial hypertension risk, and the non-clinical studies needed to discharge it should be based on the mechanism and any known class effects. The recommendation is too general.	Accepted. The evaluation of PAH and valvulopathy is considered to be an integral part of the CV safety evaluation and is briefly discussed in section 7.4. Therefore propose to delete this section.
354-356	3	This is related to our comment on section 65-74 Proposed change (if any): **Body mass index** … and obesity in adults <u>of typical body composition</u>.	Accepted.