CASE AUTH/1871/7/06

DOCTOR v SANOFI-AVENTIS

Acomplia journal advertisement

A doctor complained about an advertisement for Acomplia (rimonabant) issued by Sanofi-Aventis and published in GP. Acomplia was indicated as an adjunct to diet and exercise for the treatment of obese patients ([Body Mass Index] BMI ≥30kg/m^2), or overweight patients (BMI >27kg/m^2) with associated risk factor(s), such as type 2 diabetes or dyslipidaemia.

The complainant alleged that the advertisement was misleading and suggested that Acomplia could be used to treat all cardiometabolic risk factors associated with diseases such as diabetes mellitus and cardiovascular disease.

The suggestion that half of its effects on cardiometabolic risk factors were beyond those expected by weight alone was misleading and suggested that Acomplia had other as yet unproven effects on all cardiometabolic risk factors including those cited in its summary of product characteristics (SPC); this was not consistent with the licensed indication which was in essence to reduce weight in obese or overweight patients. If one of the consequences of this very specific use was an improvement in the overall cardiometabolic risk profile of patients then that was fine.

The advertisement implied that Acomplia had some, as yet unidentified, effect of reducing specific cardiometabolic risk factors and that it should therefore be used to treat overweight/obese patients with high-blood pressure, low HDL-c, high triglycerides, insulin resistance and abnormal inflammatory markers and HbA1c levels. What proof was there to suggest a direct and causal link between the effects of Acomplia on any of the latter parameters other than an indirect effect associated with weight reduction? If Acomplia was so effective in modulating dyslipidaemia it was paradoxical that it had no significant effect on elevated LDL-c and total-c levels, both established cardiometabolic risk factors, a fact glaringly omitted from the advertisement?

Encouraging the unlicensed use of Acomplia was further evidenced by the nonsensical statement that cardiometabolic risk factors in overweight patients could be where you least expected them. The latter clearly suggested that obesity or being overweight should not be considered as a cardiometabolic risk in isolation but should consider the effect of Acomplia on other less obvious risk factors. Thus doctors were invited to pay scant regard to the specific indication in weight reduction with the promise that Acomplia additionally modulated other independent cardiometabolic risk factors independent of weight reduction.

The complainant alleged that the advertisement exaggerated the facts which were that being overweight was a recognized cardiometabolic risk factor in its own right and that Acomplia treated only this particular parameter; any suggestion that the effects of Acomplia in modulating cardiometabolic risk factors went beyond weight reduction was patently misleading.

The Panel noted that the left hand side of the advertisement featured an outline of an overweight patient with the statement 'Cardiometabolic risk factors in overweight patients can be where you least expect them'. The right hand side was headed 'Discover Acomplia' followed by the licensed

indication. This was followed by reference to cardiometabolic risk factors, listing established risk factors as elevated blood glucose, high LDL-c and high blood pressure and emerging risk factors as low HDL-c, abdominal obesity, high triglycerides, insulin resistance and inflammatory markers. These were followed by information about reductions in weight and waist circumference. The final part of this section stated that Acomplia compared to placebo demonstrated significantly greater improvements in glycaemic control, HbA1c, increases in HDL-c and reductions in triglycerides. This was followed by the claim 'An estimated 50% of the effects of Acomplia on Cardiometabolic Risk Factors are beyond those expected from weight loss alone'.

The Panel considered that the overall impression of the advertisement was that Acomplia was to be prescribed in overweight patients because of its effects on all cardiometabolic risk factors, not that Acomplia was to be prescribed for weight management as an adjunct to diet and exercise for the treatment of obese patients and overweight patients with associated risk factors such as type 2 diabetes or dyslipidaemia. In that regard the Panel noted that the statement 'Cardiometabolic risk factors in overweight patients can be where you least expect them' appeared in very much larger type size than any of the information about weight loss. The emphasis of the advertisement was not on the licensed indication in the SPC but on the information on pharmacodynamic properties. This impression was reinforced by the strapline, 'It's not what you lose. It's what you gain'. In that regard the Panel considered that the success or otherwise of Acomplia therapy should be measured by weight loss not by alterations in cardiometabolic risk factors.

The Panel considered that there was a difference between promoting a product for a licensed indication and promoting the benefits of using that product albeit that some of the benefits were specifically mentioned in the SPC.

The licensed indication was included in the advertisement but was not the most prominent message. The Panel did not accept Sanofi-Aventis' view that the weight loss indication was clearly presented and given priority over the additional effects of Acomplia. It agreed with Sanofi-Aventis that weight loss was relatively more important in the SPC than the additional effects.

The Panel considered that the advertisement had not placed the cardiometabolic risk factors sufficiently within the context of the licensed indication. In the Panel's view the most prominent message was that Acomplia was to be prescribed for its effects on cardiometabolic risk factors in overweight patients and this was inconsistent with the SPC. A breach of the Code was ruled. This ruling was upheld on appeal by Sanofi-Aventis.

The Panel accepted that approximately 50% of the mean improvements in glycaemic control (HbA1c), HDL-c and triglycerides in patients receiving Acomplia were beyond that expected from weight loss alone. This was clearly stated in the SPC. Thus effects on some cardiometabolic risk factors beyond those expected from weight loss alone had been established. The advertisement, however, stated that 'Cardiometabolic Risk Factors include established and emerging factors…'. The Panel thus did not accept the submission that the claim 'An established 50% of the effects of Acomplia on Cardiometabolic Risk Factors are beyond those expected from weight loss alone' applied to three risk factors, HbA1c, HDL-c and triglycerides; it appeared to apply to them all. The claim was misleading in this regard and thus not capable of substantiation. Breaches of the Code were ruled. These rulings were upheld on appeal by Sanofi-Aventis.

The Panel did not consider that the circumstances justified a ruling that high standards had not been maintained. Nor did the Panel consider that the circumstances justified a ruling of a breach of Clause 2 of the Code which was reserved as a sign of particular censure. These rulings were upheld on appeal by the complainant.

A doctor complained about an advertisement for Acomplia (rimonabant) (ref RIM06/335) issued by Sanofi-Aventis that appeared in GP. According to Section 4.1 of the summary of product characteristics (SPC) Acomplia was indicated as an adjunct to diet and exercise for the treatment of obese patients ([Body Mass Index] BMI ≥30kg/m^2), or overweight patients (BMI >27kg/m^2) with associated risk factor(s), such as type 2 diabetes or dyslipidaemia. Section 4.1 referred readers to Section 5.1, pharmacodynamic properties, which included details of clinical study results.

COMPLAINT

The complainant alleged that the advertisement was misleading and suggested that Acomplia could be used to treat all cardiometabolic risk factors associated with diseases such as diabetes mellitus and cardiovascular disease.

The complainant alleged that the suggestion that half of the effects of this medicine on cardiometabolic risk factors were beyond those expected by weight alone was misleading and suggested that Acomplia had other as yet unproven effects on all cardiometabolic risk factors including those cited in its SPC; this was not consistent with the licensed indication which was in essence to reduce weight in obese or overweight patients. If one of the consequences of this very specific use was an improvement in the overall cardiometabolic risk profile of patients then that was fine.

The complainant alleged however, that this advertisement did not articulate the latter reasonable position. In fact it clearly implied that Acomplia had some magical, as yet unidentified, effect of reducing specific cardiometabolic risk factors and that it should therefore be used to treat overweight/obese patients with high-blood pressure, low HDL-c, high triglycerides, insulin resistance and abnormal inflammatory markers and HbA1c levels. What proof was there to suggest a direct and causal link between the effects of Acomplia on any of the latter parameters other than an indirect effect associated with weight reduction? Indeed, if Acomplia was so effective in modulating dyslipidaemia was it not somewhat paradoxical that it had no significant effect on

elevated LDL-c and total-c levels, both established cardiometabolic risk factors, a fact that was glaringly omitted in the advertisement?

The complainant alleged that encouraging the unlicensed use of Acomplia was further evidenced by the nonsensical statement that cardiometabolic risk factors in overweight patients could be where you least expected them. The latter clearly suggested that obesity or being overweight should not be considered as a cardiometabolic risk in isolation but should consider the effect of Acomplia on other less obvious risk factors. Thus doctors were invited to pay scant regard to the very specific indication in weight reduction with the promise that Acomplia additionally modulated other independent cardiometabolic risk factors independent of weight reduction.

The complainant alleged that surely, the requirement to take Acomplia as an adjunct to strict dietary controls and vigorous physical exercise might also have had a direct and significant effect on the improvement of many of the cardiometabolic risk factors mentioned or was it to be assumed, as the advertisement implied, that the impact of positive lifestyle improvements such as smoking cessation, daily exercise and a balanced calorie controlled diet had minimal impact in patients with diabetes or dyslipidaemia when compared with the impact of this medicine? Also what of the additive effect of the primary treatments for diabetes and dyslipidaemia such as statins, insulin, oral hypoglycaemic agents, aspirin etc, which had direct and significant positive effects on cardiometabolic risk factors that were mentioned in the advertisement or was it to be assumed that these had less of an effect compared to Acomplia.

The complainant alleged that the advertisement exaggerated the facts which were that being overweight was a recognized cardiometabolic risk factor in its own right and that Acomplia treated only this particular parameter; any suggestion that the effects of Acomplia in modulating cardiometabolic risk factors went beyond weight reduction was patently misleading.

When writing to Sanofi-Aventis the Authority asked it to respond in relation to the requirements of Clauses 2, 3.2, 7.2, 7.4 and 9.1 of the Code.

RESPONSE

Sanofi-Aventis submitted that this was the first therapeutic agent in a new class; hence it was reasonable to include some background information in the advertising in order to place this therapy in context.

The licensed indication for Acomplia as stated in the SPC was: 'As an adjunct to diet and exercise for the treatment of obese (BMI ≥30kg/m^2) or overweight (BMI >27kg/m^2) patients with associated risk factor(s), such as type 2 diabetes or dyslipidaemia (see section 5.1)'.

This clearly set out the purpose of the medicine as a treatment for obese patients or for overweight patients with additional risk factors, and incorporated into the indication a reference to the additional information on other effects of the medicine which were set out in Section 5.1 of the SPC.

The licensed indication was clearly and prominently placed at the top of the advertisement, which stated that: 'Acomplia is the first selective CB_1 blocker and is indicated for use as an adjunct to diet and exercise for the treatment of obese patients (BMI ≥30kg/m^2), or overweight patients (BMI >27kg/m^2) with associated risk factors such as type 2 diabetes or dyslipidaemia'.

Sanofi-Aventis submitted that the advertisement went on to explain that cardiometabolic risk factors included both established and emerging risk factors, which contributed to the development of type 2 diabetes and cardiovascular disease (Alberti *et al* 2005). It then listed established risk factors: elevated blood glucose, high LDL-c and high blood pressure and emerging risk factors: low HDL-c, abdominal obesity, high triglycerides, insulin resistance and inflammatory markers. No claim was made for the effect of Acomplia on these risk factors, which were referred to for explanatory purposes.

Only then did the text turn to the effects of Acomplia. Weight reduction was the first and primary area covered; there was a clear description that Acomplia demonstrated significantly greater reductions in weight and waist circumference compared with placebo (Data on file, Despres *et al* 2005). This was in accordance with the product's licensed indication.

In addition the advertisement subsequently described other observed effects of Acomplia, namely that, in comparison to placebo it demonstrated significantly greater improvements in glycaemic control (HbA1c), increases in HDL-c and reductions in triglyerides (Data on file, Despres *et al*).

Finally the advertisement stated that: 'An estimated 50% of the effects of Acomplia on cardiometabolic risk factors are beyond those expected from weight loss alone'. This statement immediately followed the bullet points relating to particular individual risk factors and hence referred specifically to them.

With regard to the allegation that Acomplia was being promoted outside of its licence including claims for effects on all cardiometabolic risk factors which were misleading and unsubstantiable, Sanofi-Aventis submitted that the licensed indication and its expression in the advertisement were discussed in detail above. The weight loss indication was clearly presented and given priority in the advertisement over the additional effects of Acomplia. This was consistent with their relative importance in the SPC.

Regarding the assertion that claims were made for all cardiometabolic risk factors, the advertisement was worded carefully to make claims only for those risk factors which were within the licence for Acomplia and for which data were available to substantiate the statements made. As stated previously, background information on the rationale for this new class of therapeutic agent was included for clarity.

With regard to the allegation that the advertisement did not emphasise the indication, ie weight loss, and did not emphasise the importance of diet and exercise in this patient population, Sanofi-Aventis submitted that the advertisement clearly described the use of Acomplia as an adjunct to diet and exercise at the outset, as stated above and did not diminish the importance of lifestyle

modification, whilst presenting the beneficial effects of the product. The intrinsic requirement for a diet and exercise regime in patients taking Acomplia was reiterated in the prescribing information. Additionally, whilst the importance of lifestyle modification was recognised, the Phase III studies included diet and exercise in both placebo and active arms, and clearly demonstrated benefit of Acomplia over and above such lifestyle modification alone.

With regard to the allegation that the picture was misleading as it did not emphasise the importance of obesity but directed attention to other risk factors, Sanofi-Aventis submitted that with regard to the figure represented in the advertisement, this highlighted the possibility that cardiometabolic risk factors in overweight patients could be where they were least expected, ie related to obesity and overweight. It did not claim or imply that established risk factors were not important, but aimed to raise awareness of the importance of obesity and overweight as being significant risk factors. This was supported by evidence from the highly regarded INTERHEART study which demonstrated that the population attributable risk for acute myocardial infarction was around 20% for abdominal obesity (Yusuf *et al* 2004) and that this was a greater level of risk than that of diabetes or hypertension for this outcome.

With regard to the allegation that the claims for Acomplia's effect beyond weight reduction were incorrect and misleading, Sanofi-Aventis submitted that the claims relating to the effect beyond weight loss were based on the outcome of the pre-specified analysis of covariance (ANCOVA) of changes in HbA1c, HDL-c and triglycerides with respect to weight loss, carried out and published in the rimonabant in obesity trials (Data on file, Despres *et al*). This analysis and these trials provided the evidence by which the statement regarding the effects beyond weight loss was validated and incorporated into the SPC. Thus the complainant's view that 'any suggestion that the effects of Acomplia in modulating cardiometabolic risk factors went beyond weight reduction was patently misleading' was incorrect.

Sanofi-Aventis submitted that although the mechanism of this effect beyond weight loss was not as yet clearly understood, pre-clinical data had provided some insight as to possible mechanisms of action. Cannabinoid CB_1 receptors had been found to have an effect in adipocytes (Bensaid *et al* 2003), hepatocytes (Osei-Hyiaman *et al* 2005), the gastrointestinal tract (Gomez *et al* 2002) and skeletal muscles (Liu *et al* 2005). The action of CB_1 receptors in these sites had been shown to effect the levels of adiponectin in adipocytes (Bensaid *et al* 2003), the expression of SREBP-1c in hepatocytes (Osei-Hyiaman *et al* 2005), to be involved in the actions of signalling systems that promote the perception of satiety in the gastrointestinal tract (Gomez *et al* 2002), and to have a role in glucose uptake in skeletal muscle (Liu *et al* 2005). However, it was important that the strength of the clinical evidence which had led to the licence indication and wording in the SPC was not confused with the evolving understanding of mechanisms of action, for a compound which was, after all, first in its class.

Sanofi-Aventis noted the complainant's allegation that the advertisement failed to recognise the beneficial effect of other licensed medicines treating various cardiometabolic risk factors. Sanofi-Aventis submitted that it was not the remit or a requirement of the advertisement to describe the beneficial effects of other products currently licensed for treatment of individual cardiometabolic risk factors. If the complainant had referred to the effect of concomitant medications in patients enrolled in the rimonabant studies, these were randomised placebo-controlled, double-blind studies designed to eliminate such bias.

Sanofi-Aventis submitted that the advertisement did not promote Acomplia in a manner inconsistent with its product license; in particular, no claims were made for the effects of Acomplia on parameters which were not referred to in the SPC and substantiated by independent research (Clause 3.2). The information, claims and comparisons accurately reflected the licence and supporting published data and were balanced in terms of appropriate reference to diet and exercise requirements (Clause 7.2); equally, they were substantiated by independent research published in peer-reviewed journals (Clause 7.4). High standards had therefore been maintained (Clause 9.1).

In conclusion, Sanofi-Aventis submitted that the advertisement clearly and responsibly described the licensed indication for Acomplia, did not mislead, misrepresent or make inappropriate claims regarding the product and satisfied the requirements of Clauses 2, 3.2, 7.2, 7.4 and 9.1 of the Code.

PANEL RULING

The Panel noted that the left hand side of the advertisement provided by Sanofi-Aventis featured an outline of an overweight patient with the statement 'Cardiometabolic risk factors in overweight patients can be where you least expect them'. The right hand side was headed 'Discover Acomplia' followed by the licensed indication. This was followed by reference to cardiometabolic risk factors listing established risk factors as elevated blood glucose, high LDL-c and high blood pressure and emerging risk factors as low HDL-c, abdominal obesity, high triglycerides, insulin resistance and inflammatory markers. These were followed by information about reductions in weight and waist circumference. The final part of this section stated that Acomplia compared to placebo demonstrated significantly greater improvements in glycaemic control, HbA1c, increases in HDL-c and reductions in triglycerides. This was followed by the claim 'An estimated 50% of the effects of Acomplia on Cardiometabolic Risk Factors are beyond those expected from weight loss alone'.

The Panel considered that the overall impression of the advertisement was that Acomplia was to be prescribed in overweight patients because of its effects on all cardiometabolic risk factors not that Acomplia was to be prescribed for weight management as an adjunct to diet and exercise for the treatment of obese patients and overweight patients with associated risk factors such as type 2 diabetes or dyslipidaemia. In that regard the Panel noted that the statement 'Cardiometabolic risk factors in overweight patients

can be where you least expect them' appeared in very much larger type size than any of the information about weight loss. The emphasis of the advertisement was not on the licensed indication as set out in Section 4.1 of the SPC but on the information in Section 5.1, pharmacodynamic properties. This impression was reinforced by the strapline, 'It's not what you lose. It's what you gain'. In that regard the Panel considered that the success or otherwise of Acomplia therapy should be measured by weight loss not by alterations in cardiometabolic risk factors.

The Panel considered that there was a difference between promoting a product for a licensed indication and promoting the benefits of using that product albeit that some of the benefits were specifically mentioned in the SPC.

The Panel noted that the licensed indication was included in the advertisement but was not the most prominent message. The Panel did not accept Sanofi-Aventis' view that the weight loss indication was clearly presented and given priority over the additional effects of Acomplia. It agreed with Sanofi-Aventis that the weight loss was relatively more important in the SPC than the additional effects.

The Panel considered that the advertisement had not placed the cardiometabolic risk factors sufficiently within the context of the licensed indication. In the Panel's view the most prominent message was that Acomplia was to be prescribed for its effects on cardiometabolic risk factors in overweight patients and this was inconsistent with the SPC. A breach of Clause 3.2 of the Code was ruled.

The Panel was unsure what was meant by the claim that cardiometabolic risk factors 'can be where you least expect them' and Sanofi-Aventis' submission that the aim was to raise awareness of the importance of obesity and being overweight as significant risk factors. In the Panel's view the intended audience would be well aware that obesity and overweight were significant risk factors. It might be that the audience would not appreciate that established risk factors in diabetes or hypertension might be less than the obesity risk factors and in this regard Sanofi-Aventis provided data in relation to the risk of acute myocardial infarction in abdominal obesity. The Panel was unsure that this message would be apparent from the claim.

The Panel accepted that approximately 50% of the mean improvements in glycaemic control (HbA1c), HDL-c and triglycerides in patients receiving Acomplia were beyond that expected from weight loss alone. This was clearly stated in Section 5.1 of the SPC. Thus effects on some cardiometabolic risk factors beyond those expected from weight loss alone had been established. The advertisement, however, stated that 'Cardiometabolic Risk Factors include established and emerging factors…'. The Panel thus did not accept the submission that the claim 'An established 50% of the effects of Acomplia on Cardiometabolic Risk Factors are beyond those expected from weight loss alone' applied to three risk factors, HbA1c, HDL-c and triglycerides; it appeared to apply to them all. The claim was misleading in this regard and thus not capable of substantiation.

Breaches of Clauses 7.2 and 7.4 were ruled.

The Panel did not consider that the circumstances justified a ruling of a breach of Clause 9.1 and ruled accordingly. Nor did the Panel consider that the circumstances justified a ruling of a breach of Clause 2 which was reserved as a sign of particular censure.

APPEAL BY SANOFI-AVENTIS

Sanofi-Aventis appealed the Panel's rulings of breaches of Clauses 3.2, 7.2 and 7.4. In summary, Sanofi-Aventis submitted that:

- Obesity was a serious medical condition that caused health problems such as diabetes and heart disease. Treatment aimed to reduce morbidity and mortality through reducing weight and improving risk factors.
- The advertisement was intended to convey an important educational message regarding the modern understanding of obesity and its management, in addition to introducing Acomplia.
- The Panel's ruling was based on an understanding that Acomplia was indicated for weight management. However, the actual indication was for the treatment of obese patients or overweight patients with associated risk factors, in keeping with the modern understanding of obesity as a disease.

Sanofi-Aventis explained that the understanding of obesity as a disease had advanced considerably in the last decade. Even small degrees of weight loss in patients with an increased risk of cardiovascular disease led to a significant reduction in the risk to health, through improvement in multiple cardiometabolic risk factors and a demonstrable reduction in the incidence of cardiovascular events (Eilat-Adar *et al* 2005). The definition of treatment success was now accepted as modest weight loss (as little as 5% of body weight in a moderately overweight patient) accompanied by improvements in risk factors for cardiovascular and metabolic disease.

Sanofi-Aventis submitted that fat tissue was not an inert storage organ but was highly dynamic, involved in a diverse range of physiological and metabolic processes, and responsible for the production of over fifty adipokines – proteins with signalling properties and functional roles that included energy balance, insulin sensitivity and lipid metabolism (Ronti *et al* 2006). Therefore many adverse effects were amplified when fat tissue was present in excess. Finally, there was a clear understanding of the long-recognised observation that the location of fat tissue was important in respect to adverse effects – fat tissue in the abdomen was more active metabolically than subcutaneous fat and was particularly linked to ill health (Després *et al* 2001).

Sanofi-Aventis submitted that these recent advances in medical science underpinned the current rationale for treating obesity as a disease. As obesity pre-disposed to both metabolic and cardiovascular comorbidities (such as type 2 diabetes and cardiovascular disease), the aim of treatment was to achieve realistic gradual weight loss and prevent the morbidity and mortality associated with obesity,

without undue adverse effects. (Atterburn and Noel 2004). Patients in whom treatment was particularly indicated were those with comorbidities such as coronary heart disease and diabetes.

Sanofi-Aventis submitted that the advertisement was intended to ensure that Acomplia was used responsibly by health professionals, reinforcing the concept that in patients who were overweight or obese, intervention was best reserved for those whose condition was complicated by comorbidities. A significant component of the advertisement was devoted to informing readers about the association between obesity and cardiometabolic risk factors, the understanding of which was central to the modern paradigm of disease management. The intent of the red man graphic and statements on cardiometabolic risk factors being where you least expect them were to raise awareness that obesity was not a cosmetic condition, but could be a serious medical condition implicated in the development of risk factors for cardiovascular and metabolic disease.

Sanofi-Aventis noted Acomplia was indicated (Section 4.1 of the SPC) 'As an adjunct to diet and exercise for the treatment of obese patients (BMI ≥30kg/m^2), or overweight patients (BMI >27kg/m^2) with associated risk factor(s), such as type 2 diabetes or dyslipidaemia (see Section 5.1)'. There was no mention of weight or weight management in this indication. Effects on weight were instead presented alongside those on other cardiometabolic risk factors (specifically those listed in the advertisement HDL-c, triglycerides and glycaemic control as assessed by HbA1c). This was in contrast to earlier treatments for obesity – for example, Reductil (sibutramine), another agent for the treatment of obesity which was licensed five years before Acomplia, had an indication that specifically referred to weight management (Reductil SPC).

Sanofi-Aventis submitted that this background underpinned the basis on which it was appealing the Panel's rulings. To summarise the points under consideration, the complainant made allegations that included the following:

- The advertisement suggested that weight should not be considered in isolation and that other risk factors should be considered important in obese/overweight patients, which were not in keeping with the 'very specific indication for Acomplia' of 'weight reduction'.
- There was no evidence to support the claim that Acomplia had any effects beyond weight loss.

Sanofi-Aventis noted that with respect to these allegations, the Panel had made the following observations:

Firstly, the Panel had decided that taken as a whole, the advertisement had not given the impression that Acomplia was to be prescribed for an indication of weight management, noting that the advertisement did not appear to be in support of the licensed indication set out in Section 4.1 of the SPC, but based around information on other benefits provided in Section 5.1. A breach of Clause 3.2 had been ruled.

Sanofi-Aventis appealed the ruling on the basis that weight management *per se* was not the licensed indication for Acomplia. The SPC clearly stated in Section 4.1 that Acomplia was indicated for the treatment of obese and overweight patients; there was no mention of weight or weight management in this indication (Acomplia SPC). Whilst not specifically referred to in the indication (Section 4.1), the efficacy of Acomplia in both weight management and on cardiometabolic risk factors were all contained in Section 5.1 of the SPC, to which Section 4.1 referred. These effects were all described within the advertisement, and presented in the order in which they were listed in the SPC (this interpretation of the licence was developed and agreed during discussion with the Medicines and Healthcare products Regulatory Agency prior to launch).

Sanofi-Aventis submitted that the aim of medical management of these conditions was to reduce the burden of metabolic or cardiovascular disease, not simply to reduce weight. Sanofi-Aventis understood that the Panel had perceived weight management to be the indication (Section 4.1of the SPC), and had made its rulings based on this. Sanofi-Aventis considered that expressing all the benefits of the product was in keeping with the requirements of the Code, and that through its ruling the Panel was giving direction to limit promotion to only a portion of the information within Section 5.1 (weight management), rather than allowing all of the detail within Section 5.1 of the SPC to be presented.

Secondly, the Panel had decided that the claim 'An estimated 50% of the effects of Acomplia on Cardiometabolic Risk Factors are beyond those expected from weight loss alone' appeared to apply to more than the risk factors listed in the advertisement and was therefore misleading in breach of Clauses 7.2 and 7.4. The Panel had accepted that with respect to improvements in the risk factors listed, this claim was accurate and clearly presented in the SPC.

Sanofi-Aventis appealed this ruling on the basis that the statement 'An estimated 50% of the effects of Acomplia on Cardiometabolic Risk Factors are beyond those expected from weight loss alone' was not a claim that Acomplia reduced risk factors. It was simply a qualifying statement that outlined how much of an effect was due to weight loss in those risk factors on which Acomplia had an effect. As this was a qualifying statement, it could only make sense if the benefits of Acomplia on risk factors were known, and these were clearly presented adjacent to this additional piece of information.

Sanofi-Aventis submitted in conclusion that this advertisement had been produced with the aim of informing readers about the links between obesity and serious medical conditions and to encourage responsible prescribing (ie restricted to a cohort of patients who were obese or overweight but with associated risk factors). Preliminary results from a drug utilisation study suggested that this approach resulted in rational use of Acomplia in the UK, with use in a BMI < 30kg/m^2 in the absence of a comorbid condition being found in only 3 out of 338 patient records that had been studied. Overall, a high proportion of all patients studied had been found to have one or more additional risk factors for cardiovascular or metabolic disease.

COMMENTS FROM THE COMPLAINANT

The complainant stated that it was patronising to suggest that most physicians were not cognisant of the modern understanding of obesity and its management. It was widely recognised that it was primarily the clinical effect of weight reduction that led to improving cardiometabolic risk factors. This was not what the advertisement conveyed for all of the reasons previously outlined. If the purpose was not to promote off-licence and extrapolate to include unlicensed effects, then might one ask why in the advertisement reductions in weight and waist circumference, cardiometabolic risk factors appropriately associated with the licensed clinical effect of Acomplia ie weight loss, appeared in a conspicuous red typeset and directly associated with improvements in glycaemic control, increases in HDL-c and reductions in triglycerides which were also in red type? Was this not an example of marketing aimed at the unsuspecting reader?

The complainant alleged that the assertion that the product indication made no mention of weight or weight management was patently absurd given that it did mention the terms 'obese patients, BMI >27kg/m^2 and overweight patients'. Could Sanofi-Aventis advise physicians in need of education precisely how they were to identify obese and overweight patients for treatment with Acomplia and in keeping with the wording of the SPC if not by first measuring their weight and then identifying any other associated risk factor(s)?

Indeed if one was to refer to the specific wording in the SPC then what did Sanofi-Aventis have to say with regards to the fact that the SPC clearly indicated that the only effect relevant to prescribers with respect to Acomplia's licensed indication was in fact 'weight loss' by use of the wording 'The clinical effect (weight loss) of rimonabant…'.

The complainant considered that Sanofi-Aventis' appeal was a cynical attempt to prolong the use of the advertisement.

APPEAL BOARD RULING

The Appeal Board agreed with the Panel's view that the emphasis in the advertisement was on cardiometabolic risk factors. In addition the Appeal Board noted that the generally accepted definition of 'overweight' was BMI >25kg/m^2. Although the Acomplia SPC stated it was indicated for use in overweight patients such patients had to have a BMI >27kg/m^2 and associated risk factors such as type 2 diabetes or dyslipidaemia. This was not sufficiently clear in the advertisement. The prominent statement on the left hand part of the advertisement 'Cardiometabolic risk factors in overweight patients' implied that Acomplia could be used in all overweight patients with cardiometabolic risk factors which was not so. There were a group of patients (BMI >25kg/m^2 <27kg/m^2) for whom Acomplia was not indicated. The detail was given in smaller print on the right hand part of the advertisement.

The Appeal Board considered that the inclusion in the advertisement of an outline of an overweight patient with the statement that cardiometabolic risk factors were 'where you least expect them' over their waist, drew attention to abdominal obesity. The Appeal Board noted Sanofi-Aventis' submission regarding the differences between abdominal fat and subcutaneous fat and that abdominal obesity was a cardiovascular risk factor in its own right. The Appeal Board noted that it was possible for a person to be abdominally obese but to still have a BMI <27kg/m^2. Acomplia was to be prescribed according to a patient's BMI and, if this was above 27kg/m^2 and below 30kg/m^2, then the patient needed to have associated risk factors such as type 2 diabetes or dyslipidaemia; abdominal obesity *per se* was not the reason to prescribe.

Overall, the Appeal Board considered that the advertisement had not placed the cardiometabolic risk factors sufficiently in the context of the licensed indication. Thus the Appeal Board upheld the Panel's ruling of a breach of Clause 3.2. The appeal on this point was unsuccessful.

The Appeal Board accepted that approximately 50% of the beneficial effects in glycaemic control (HbA1c), HDL-c and triglycerides in patients receiving Acomplia were beyond that expected from weight loss alone. This was clearly stated in Section 5.1 of the SPC. Thus effects on some cardiometabolic risk factors beyond those expected from weight loss alone had been established. The advertisement mixed information about cardiometabolic risk factors with promotional messages about Acomplia. Readers were told that 'Cardiometabolic Risk Factors include established and emerging factors …' and then given a list of such risk factors. At the end of that particular section of text, and in the same type size and font 'Cardiovascular Risk Factors' were again referred to. The Appeal Board considered that readers would thus assume that the statement 'An estimated 50% of the effects of Acomplia on Cardiometabolic Risk Factors are beyond those expected from weight loss alone' encompassed all of the foregoing cardiometabolic risk factors and not the final three as submitted by Sanofi-Aventis. The claim was misleading in this regard and thus not capable of substantiation. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.4. The appeal on this point was unsuccessful.

APPEAL BY THE COMPLAINANT

The complainant appealed the Panel's rulings of no breach of Clauses 2 and 9.1.

The complainant was encouraged by the findings but surprised that these misleading advertisements continued to appear in a myriad of journals. Surely, given the Panel's rulings, these needed to be promptly withdrawn? The complainant was particularly concerned about this because he was now also aware that this misleading information was not restricted to the advertisements but was also being peddled by certain Sanofi-Aventis sponsored physicians. There was no doubt that this misleading information was being used by the company representatives and that all of these activities had occurred in the full knowledge of the company's senior management. The complainant urged the Appeal Board to look into the whole programme of how Sanofi-Aventis

promoted Acomplia beyond the advertisements.

The complainant alleged that the continued dissemination of this misleading information, which was inconsistent with the licensed indication of Acomplia, was testament to the fact that Sanofi-Aventis had and continued to bring the pharmaceutical industry into disrepute. If ever a sign of particular censure was mandated then surely this was an example of where it should be applied. The complainant understood that, the Panel had previously made very similar and clear rulings about the promotion of other newly launched anti-obesity drugs. Did it not occur to Sanofi-Aventis to learn from these past precedents? Clearly not; which was why it had also failed to take the necessary steps to maintain high standards.

The complainant was unconvinced that the Appeal Board had any real power to bring such negligent activity to book but it at least provided a minimum avenue for concerns to be aired. Finally, the complainant stated that he was not motivated by a pathological dislike of the industry; in fact he was positively predisposed towards the important role it had to play in the delivery of real health improvements. However, until the sort of activity undertaken by Sanofi-Aventis was addressed seriously then there would always be a climate of scepticism towards the pharmaceutical industry.

COMMENTS FROM SANOFI-AVENTIS

Sanofi-Aventis noted that the complainant's appeal appeared to make the following points:

- This advertisement, and associated items within the promotional campaign, were still in use despite the initial ruling of the Panel.
- This activity brought the industry into disrepute, as Sanofi-Aventis was not maintaining high standards (Clause 9.1), and deserved particular censure (Clause 2).

Sanofi-Aventis submitted that its response could only be made with reference to the original complaint. In its ruling, the Panel considered that there was widespread understanding of obesity as a risk factor for cardiovascular and metabolic disease. Sanofi-Aventis submitted that emerging risk factors were not widely appreciated – a 2006 survey showed that only around a third of doctors recognised abdominal obesity and a quarter recognised HDL-c /triglycerides as risk factors in their own right. Providing education around these risk factors was therefore meeting a true need with respect to education. Education such as this was a positive component of promotional material, and rather than being a sign of poor standards and deserving particular censure, this was an activity that actually highlighted a positive contribution to improving health, one of the industry's primary objectives. On this basis, the company strongly disagreed with the complainant's suggestion that high standards had not been maintained and that this activity was a discredit to the industry.

Sanofi-Aventis noted the complainant's suggestion that it had not learnt from previous companies' activities in this therapeutic area. Whilst recognising that a previous ruling could only be judged on its own merits, the most relevant case appeared to be concerned with the promotion of use in groups of patients with risk factors that were specifically contraindicated (Case AUTH/1197/6/01). The company agreed with the interpretation of the Panel at the time that this was inappropriate, on the basis that this compromised patient safety by encouraging inappropriate prescribing. However, this was not relevant to the Acomplia advertisement as it did not suggest that the product be used in any contraindicated condition, and neither had this been suggested by either the complainant or Panel.

In summary, Sanofi-Aventis agreed with the Panel's original decision that high standards had been maintained throughout and that there was no activity warranting particular censure.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant countered the fallacious argument that an advertisement was an appropriate and responsible platform from which to 'provide education' on a topic which often filled entire chapters and textbooks. Had this advertisement been an advertorial one might have conceded this suggestion but how did an A3 sized advertisement comprising in the main a red silhouette of an obese individual constitute education?

APPEAL BOARD RULING

The Appeal Board, although noting its ruling above, did not consider that the circumstances justified a ruling of a breach of Clause 9.1 of the Code and it thus upheld the Panel's ruling of no breach. Nor did the Appeal Board consider that the circumstances justified a ruling of a breach of Clause 2 which was reserved as a sign of particular censure. The Appeal Board upheld the Panel's ruling of no breach of Clause 2. The appeal on this point was unsuccessful.

Complaint received **27 July 2006**

Case completed **7 November 2006**