GENERAL PRACTITIONER/DIRECTOR v SANOFI-AVENTIS

Acomplia journal advertisement

A general practitioner complained about an advertisement for Acomplia (rimonabant) produced by Sanofi-Aventis and published in Update. As this involved an alleged breach of undertaking, that element of the case was taken up by the Director as it was the responsibility of the Authority to ensure compliance with undertakings.

The complainant stated that the advertisement identified HbA1c, HDL-C and triglycerides as cardiometabolic risk factors. It also stated that, in addition to improvements in weight, Acomplia demonstrated significantly greater improvements in these particular cardiometabolic risk factors. The statement clearly suggested that Acomplia had a direct effect on these cardiometabolic risk factors independent of weight reduction. The advertisement continued 'An estimated 50% of the effects of Acomplia on these Cardiometabolic Risk Factors are beyond those expected from weight loss alone'.

The complainant alleged that the advertisement was misleading as it invited doctors to prescribe Acomplia outside its specific indication for treating obesity in patients with associated risk factors such as type 2 diabetes and dyslipidaemia ie for the primary and sole purpose of addressing HbA1c, HDL-C and triglycerides. There was no evidence to show that Acomplia had a direct effect on these cardiometabolic risk factors as opposed to an indirect effect mediated through weight reduction. Was it reasonable for an advertisement to invite unfounded speculation as to where the other 50% of the effect of Acomplia on cardiometabolic risk factors arose from?

The complainant alleged that the advertisement was misleading as it implied that HbA1c, HDL-C and triglycerides were the only markers of cardiometabolic risk that were relevant and needed to be addressed in obese patients with diabetes or dyslipidaemia. Total-C and LDL-C were also well recognized important cardiometabolic risk factors, however the impact of Acomplia on these was not referred to. Could this be due to the fact that the summary of product characteristics (SPC) stated that generally Acomplia 20mg had no significant effect on Total-C or LDL-C levels. Surely this omission was misleading given the emphasis on the importance of addressing cardiometabolic risk factors and the positive effect of Acomplia on these?

The Panel considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very important for the reputation of industry that companies complied with undertakings.

The Panel noted that the advertisement at issue in the previous case, Case AUTH/1871/7/06, 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'. In Case AUTH/1871/7/06, the Panel (and upon appeal by Sanofi-Aventis, the Appeal Board) had 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 which was upheld on appeal. The Panel 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 had been ruled which on appeal by Sanofi-Aventis were upheld.

The advertisement at issue in the present case, Case AUTH/1976/3/07, featured an outline of an overweight person with the prominent claim 'In obese patients cardiometabolic risk factors can increase the problem'. Adjacent text introduced Acomplia by reference to its licensed indication. Reference was made to the impact of obesity on cardiometabolic risk factors which contributed to the development of type-2 diabetes and cardiovascular disease. The final paragraph

discussed improvements in three cardiometabolic risk factors: improvements in glycaemic control: increases in HDL-C and reductions in triglycerides and concluded 'An estimated 50% of the effects of Acomplia on these Cardiometabolic Risk Factors are beyond those expected from weight loss alone'. A strapline beneath the product logo in the bottom right-hand corner of the advertisement read 'It's not what you lose. It's what you gain'.

The Panel considered that the advertisement was materially different to that considered in Case AUTH/1871/7/06. The prominent claim superimposed over the outline of the overweight patient began 'In obese patients …' thus making the patient population clear at the outset. The final paragraph made it clear that the cardiometabolic risk factors were those three listed. The Panel considered the changes to the present advertisement were such that it was not caught by the undertaking given in the previous case. No breach of the Code was ruled.

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 these benefits were mentioned in the SPC.

Overall, the Panel did not accept that the advertisement invited the prescription of Acomplia for the primary and sole purpose of addressing of HbA1c, HDL-C and triglycerides as alleged. The prominent claim 'In obese patients cardiometabolic risk factors can increase the problem' made the patient population clear. The adjacent text began by stating the licensed indication at the outset. Obesity was described as having an impact on multiple cardiometabolic risk factors. The Panel queried whether the strapline 'It's not what you lose. It's what you gain' gave sufficient emphasis to weight loss. Nonetheless on balance the Panel considered that the overall tone of the advertisement placed the cardiometabolic risk factors sufficiently within the context of Acomplia's licensed indication. No breach of the Code was ruled.

The Panel did not consider that the advertisement misleadingly stated or implied that those cardiometabolic risk factors mentioned were the only ones relevant and needed to be addressed in obese patients with diabetes or dyslipidaemia. Nor did the Panel consider that the failure to refer to the statement in the Acomplia SPC that, 'Generally Acomplia 20mg had no significant effect on Total-C or LDL-C levels' was misleading as alleged. No breach of the Code was ruled.

A general practitioner complained about a journal advertisement (ref ACO 07/1049) for Acomplia (rimonabant) produced by Sanofi-Aventis and published in Update, March 2007. As this case involved an alleged breach of undertaking, that element of the case was taken up by the Director as it was the responsibility of the Authority to ensure compliance with undertakings.

COMPLAINT

The complainant stated that the advertisement identified HbA1c, HDL-C and triglycerides as cardiometabolic risk factors. It also stated that, in addition to improvements in weight, Acomplia demonstrated significantly greater improvements in these particular cardiometabolic risk factors. The statement clearly suggested that Acomplia had a direct effect on these cardiometabolic risk factors independent of weight reduction.

The advertisement continued by claiming that 'An estimated 50% of the effects of Acomplia on these Cardiometabolic Risk Factors are beyond those expected from weight loss alone'.

The complainant alleged that the advertisement was misleading as it invited doctors to prescribe Acomplia outside its specific indication for treating obesity in patients with associated risk factors such as type 2 diabetes and dyslipidaemia ie for the primary and sole purpose of addressing HbA1c, HDL-C and triglycerides. The latter suggestion was also invited by the wording that some of its effects were due to effects beyond those expected from weight loss alone.

There was no evidence to show that Acomplia had a direct effect on these cardiometabolic risk factors as opposed to an indirect effect mediated through weight reduction.

Was it reasonable for an advertisement to invite unfounded speculation as to where the other 50% of the effect of Acomplia on cardiometabolic risk factors arose from? If this was acceptable then it would seem reasonable for the statins to promote their many well documented plieotropic effects outside their specific indications?

The complainant alleged that the advertisement was misleading as it implied that HbA1c, HDL-C and triglycerides were the only markers of cardiometabolic risk that were relevant and needed to be addressed in obese patients with diabetes or dyslipidaemia. Total-C and LDL-C were also well recognized important cardiometabolic risk factors, however the impact of Acomplia on these was not referred to. Could this be due to the fact that the summary of product characteristics (SPC) stated that generally Acomplia 20mg had no significant effect on Total-C or LDL-C levels. Surely this omission was misleading given the emphasis on the importance of addressing cardiometabolic risk factors and the positive effect of Acomplia on these?

When writing to Sanofi-Aventis, the Authority asked it to respond in relation to Clauses 7.2 and 7.4 of the Code and, in addition, to Clauses 2, 9.1 and 22.

RESPONSE

Sanofi-Aventis noted that the complainant raised an issue that the Authority had already considered, ie the claim that 'An estimated 50% of the effects of

Acomplia … are beyond those expected from weight loss alone'. The question as to whether this claim was acceptable arose in Case AUTH/1871/7/06, and Sanofi-Aventis provided information that supported this claim, which was a quotation from the marketing authorization. Although the Panel accepted that this statement was firmly evidence-based and acceptable with respect to three risk factors (HbA1c, HDL-C and triglycerides), the lack of an explicit link between the statement and these three risk factors was found to be a fault. With this in mind, the advertisement now at issue made this explicit link - the list of three risk factors was followed immediately by the claim 'An estimated 50% of the effects of Acomplia **on these cardiometabolic risk factors** are beyond those expected from weight loss alone' [emphasis added by Sanofi-Aventis]. Sanofi-Aventis believed that this amendment removed all ambiguity as to the weight-independent effects of Acomplia. It had previously been accepted that this claim was capable of substantiation (in accordance with Clauses 7.2 and 7.4), and the text had been specifically amended to address the shortcomings in the previous case (in accordance with Clause 22). Sanofi-Aventis was satisfied therefore that in this respect high standards had been maintained.

Sanofi-Aventis noted that the complainant was concerned that the advertisement sought to position Acomplia as a treatment for risk factors in the absence of obesity, by virtue of the fact that it 'invited doctors to prescribe Acomplia outside its specific indication for treating obesity in patients with associated risk factors', partly in light of the statement regarding the effects on risk factors being partially independent of weight loss (although this had been deemed acceptable). This was related to the complaint in Case AUTH/1871/7/06 in which it was considered that a previous advertisement implied that Acomplia was to be prescribed for its effects on risk factors rather than obesity; the current advertisement addressed these shortcomings. Sanofi-Aventis did not agree that the advertisement sought to encourage prescription in non-obese patients because:

- The product licence specifically identified patients (body mass index (BMI) 27-30kg/m^2) with risk factors (such as type 2 diabetes and dyslipidaemia) as being the specific population in whom the product was indicated. In view of this, Sanofi-Aventis considered it appropriate and essential to discuss risk factors - indeed a failure to do so would leave it open to the criticism that it was seeking to promote outside of the licensed indication by failing to draw attention to a patient group in whom the presence of risk factors was an absolute prerequisite to treatment.
- In contrast to the previous advertisement, the current advertisement had a primary focus on obesity. Following criticism of the previous banner headline in which 'Cardiometabolic Risk Factors' was the initial and most prominent text, this had been re-worked to open with the phrase 'In Obese Patients', making obesity the most prominent message and the focus of this advertisement. This sentence continued to refer to cardiometabolic risk factors, but this mention was specifically linked to obesity.
- The uppermost text on the right hand side of the page outlined the indication in accordance with the marketing authorization, and was followed by a sentence outlining the effect that obesity had on cardiometabolic risk factors.
- Below this, the effects of Acomplia were outlined, initially on weight (as its primary effect), and then on the three cardiometabolic risk factors referred to in the licence, agreed to be acceptable in the previous case (Case AUTH/1871/7/06). These effects were again specifically expressed in the context of being in addition to the effects of weight, indicating that this was in the primary context of the treatment of obesity.
- There was no mention of effect on cardiometabolic risk factors in isolation (ie outside of the context of treatment of obesity/weight reduction).

In summary, this advertisement had been re-written with the focus on obesity and weight loss as the primary message, in accordance with both the SPC and the findings of the Panel in respect to the previous version. These were now the leading messages in all sections of the advertisement, and in particular obesity was the most prominent component of the banner headline. Most importantly, there was no mention of cardiometabolic risk factors without these having been prefaced by statements on obesity or weight - these being an essential requirement for treatment in patients with a BMI 27-30kg/m^2. For these reasons Sanofi-Aventis disagreed that this advertisement promoted Acomplia for the treatment of risk factors in the absence of obesity - the very opposite was stated in the first paragraph of text (where treatment was advocated in accordance with the licence on the basis of BMI plus or minus risk factors). Sanofi-Aventis believed that this advertisement was consistent with the product licence, took into account the undertaking to comply with the findings of Case AUTH/1871/7/06 (in accordance with Clause 22), and that high standards had been maintained.

Finally, Sanofi-Aventis noted that the complainant suggested that omission of risk factors other than the three in the advertisement, misleadingly implied that Acomplia was to be used for the treatment of all risk factors. This opinion was contrary to that of the Panel in Case AUTH/1871/7/06, in which it was decided that the mention of risk factors beyond the three in the SPC implied that Acomplia would have effects on all risk factors. The criticism that the original extended list was misleading had been addressed by removing reference to risk factors other than the three specifically affected by Acomplia. This would be expected to address the concerns of the Panel, but had now given rise to criticism that the list of three risk factors was misleading through being too short. Faced with these contradictory opinions, Sanofi-Aventis considered that its decision to remove reference to all risk factors other than the three mentioned above was a responsible and reasonable approach, as this was consistent with the SPC and addressed the Panel's concerns in Case AUTH/1871/7/06. It would be impractical to include a list of risk factors unaffected by Acomplia - as would be the case with all medicines

a list of conditions or parameters upon which no effect had been demonstrated would be of prohibitive length, and there would be no rational basis to select a shortened list from these. With this respect, Sanofi-Aventis again considered that the advertisement was consistent with the product licence, took into account the undertaking to comply with the findings of Case AUTH/1871/7/06 (in accordance with Clause 22), and that high standards had been maintained.

In conclusion, Sanofi-Aventis believed that the advertisement in question was consistent with the product licence, all claims regarding Acomplia were substantiable (entirely by data contained within the SPC), and most importantly it took into account the outcome of Case AUTH/1871/7/06. In view of this, Sanofi-Aventis was confident that no breach of Clauses 7.2, 7.4 or 22 had occurred, that high standards had been maintained throughout and that there was no reason for particular censure.

PANEL RULING

The Panel considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very important for the reputation of industry that companies complied with undertakings.

The Panel noted that the advertisement at issue in the previous case, Case AUTH/1871/7/06, 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'. In Case AUTH/1871/7/06, the Panel (and upon appeal by Sanofi-Aventis, the Appeal Board) had 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 which was upheld on appeal. The Panel 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 which were upheld on appeal.

The advertisement at issue in the present case, Case AUTH/1976/3/07, featured an outline of an overweight person with the prominent claim 'In obese patients cardiometabolic risk factors can increase the problem'. Adjacent text introduced Acomplia by reference to its licensed indication. Reference was made to the impact of obesity on cardiometabolic risk factors which contributed to the development of type-2 diabetes and cardiovascular disease. The final paragraph discussed improvements in three cardiometabolic risk factors: improvements in glycaemic control: increases in HDL-C and reductions in triglycerides and concluded 'An estimated 50% of the effects of Acomplia on these Cardiometabolic Risk Factors are beyond those expected from weight loss alone'. A strapline beneath the product logo in the bottom right-hand corner of the advertisement read 'It's not what you lose. It's what you gain'.

The Panel considered that the advertisement at issue was materially different to that considered in Case AUTH/1871/7/06. The prominent claim superimposed over the outline of the overweight patient began 'In obese patients …' thus making the patient population clear at the outset. The final paragraph made it clear that the cardiometabolic risk factors were those three listed. The Panel considered the changes to the present advertisement were such that it was not caught by the undertaking given in the previous case. No breach of Clause 22, and thus Clauses 9.1 and 2 was ruled.

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 these benefits were mentioned in the SPC.

Section 5.1 of the SPC referred to a study in type 2 diabetic patients who were overweight or obese which estimated that approximately half of the mean improvement in HbA1c in patients receiving Acomplia 20mg was beyond that expected from weight loss alone. In the non-diabetic study it was estimated that approximately half of the observed improvement in HDL-C and triglycerides in patients who received Acomplia 20mg was beyond that expected from weight loss alone.

Overall, the Panel did not accept that the advertisement invited doctors to prescribe Acomplia for the primary and sole purpose of addressing of HbA1c, HDL-C and triglycerides as alleged. The prominent claim 'In obese patients cardiometabolic risk factors can increase the problem' made the patient population clear. The adjacent text began by stating the licensed indication at the outset. Obesity was described as having an impact on multiple cardiometabolic risk factors. The Panel queried whether the strapline 'It's not what you lose. It's what

you gain' gave sufficient emphasis to weight loss. Nonetheless on balance the Panel considered that the overall tone of the advertisement placed the cardiometabolic risk factors sufficiently within the context of Acomplia's licensed indication. No breach of Clauses 7.2 and 7.4 was ruled.

The Panel did not consider that the advertisement misleadingly stated or implied that those cardiometabolic risk factors mentioned were the only ones relevant and needed to be addressed in obese patients with diabetes or dyslipidaemia. Nor did the Panel consider that the failure to refer to the statement in the Acomplia SPC that, 'Generally Acomplia 20mg had no significant effect on Total-C or LDL-C levels' was misleading as alleged. No breach of Clauses 7.2 and 7.4 was ruled.

Complaint received **15 March 2007**

Case completed **21 May 2007**