CASE AUTH/2324/6/10

PFIZER v JOHNSON & JOHNSON

Promotion of Nicorette

Pfizer complained about a slide entitled 'Stapleton: Combination Success Rates at 4 weeks' within a Nicorette (nicotine transdermal patch) presentation issued by Johnson & Johnson entitled 'Hitting "Hard to Reach Targets" with High Dose & Combination NRT [nicotine replacement therapy]'. Pfizer produced Champix (varenicline).

The slide in question was referenced to Stapleton *et al* (2008) (the published paper was dated 2007). The first bullet point read, 'Evaluation of consecutive routine cases before and after the introduction of varenicline (N=412)' and appeared above a bar chart headed 'Abstinence rates at 4 weeks'. The bar chart stated to be adapted from Stapleton *et al* (2008) compared the percentage abstinence rates of combination NRT (66.3%) with varenicline (72.1%). Between the bars appeared 'ns*'. Two bullet points beneath the bar chart read '2 out of 3 smokers on combination NRT were abstinent at 4 weeks' and 'No statistically significant difference between combination NRT and varenicline*'. The two asterisks led the reader to a small footnote at the bottom of the slide which read 'Evaluation not designed to detect a difference between combination NRT and varenicline'.

Pfizer noted that Stapleton *et al* discussed the short-term smoking cessation rates for varenicline, single NRT and combination NRT. The authors concluded that '… we observed little difference between the efficacy of varenicline and combination NRT therapy …' they also stated '… although this evaluation was not designed with adequate statistical power to test this'. Although a small footnote to this effect appeared on the slide, the Code stated that 'In general, claims should not be qualified by the use of footnotes and the like'. Pfizer considered that overall the slide implied that there was no significant difference between varenicline and combination NRT smoking cessation therapies even though the authors explicitly stated that the study was not statistically powered to detect this. Johnson & Johnson argued that the observation of 'no statistically significant difference between NRT and varenicline' was acceptable as a standalone claim and presumably therefore did not require further clarification or qualification. Pfizer contested this assertion.

Pfizer further submitted that the slide clearly represented an attempt to mislead the audience as to the meaning of this result, otherwise why show it at all if the only thing to be demonstrated was that a study which was not designed or powered to show any difference did, indeed, fail to show any difference? It was clearly an attempt to lead the audience to believe that there was no difference in efficacy between varenicline and combination NRT treatment, something which this study was not designed to, and did not, demonstrate.

Pfizer was also concerned that the slide failed to mention that the aforementioned observation was not the primary endpoint of Stapleton *et al*. The authors stated that 'The results suggest that, with routine psychological and behavioural group support, varenicline is more effective than NRT in aiding short-term smoking cessation'. Due to this omission the slide did not fully and accurately reflect the authors' concluding views.

As a result, the slide was misleading regarding the design and results of the study and in particular the details of equivalent efficacy for combination NRT and varenicline in short-term smoking cessation.

The detailed response from Johnson & Johnson is given below.

The Panel noted that Stapleton *et al* compared the effectiveness of varenicline with NRT for smoking cessation and evaluated the safety and effectiveness of varenicline in people with mental illness. The authors stated that 'Varenicline was significantly more effective than single-product NRT therapy and increased cessation rates by about 14% … However, there was no evidence of a difference in success rates between varenicline and combination NRT'. In the discussion section the authors further stated that 'The results suggest that, with routine psychological and behavioural group support, varenicline is more effective than NRT in aiding short-term smoking cessation' and 'Interestingly, we observed little difference between the efficacy of varenicline and combination NRT therapy, although this evaluation was not designed with adequate statistical power to test this'. The authors concluded that 'In this setting and with group support varenicline appears to improve success rates over those achieved with NRT …'.

The Panel noted that the slide in question was part of a presentation about high dose and combination NRT in hard to reach targets. The Panel noted Johnson & Johnson's submission that the data at issue was important and highly relevant to those working in smoking cessation. It was currently the only published data comparing varenicline and combination NRT. Nonetheless the presentation of such data had to comply with the Code. The information had to be sufficiently complete such as to allow clinicians to form their own opinion of the therapeutic value of the data presented.

In the Panel's view the design and content of the

slide implied that Stapleton *et al* was powered to detect a difference between varenicline and combination NRT and that was not so. The Panel considered that the footnote was insufficient to negate the misleading impression about the validity of the comparison and the power of the study. The slide was misleading in this regard as alleged; high standards had not been maintained. Breaches of the Code were ruled.

The Panel noted that the presentation discussed high dose and combination NRT in hard to reach targets. The slide in question presented the combination NRT data vs varenicline. The Panel did not consider that the slide was misleading because it omitted reference to other outcomes from Stapleton *et al* as alleged. No breach of the Code was ruled.

Pfizer Limited complained about a slide entitled 'Stapleton: Combination Success Rates at 4 weeks' within a Nicorette (nicotine transdermal patch) presentation issued by Johnson & Johnson Limited and entitled 'Hitting "Hard to Reach Targets" with High Dose & Combination NRT [nicotine replacement therapy]' (ref 05607). Pfizer produced Champix (varenicline). Inter-company dialogue had failed to resolve the matter.

The slide was referenced to Stapleton *et al* (2008) (the published paper was dated 2007). The first bullet point read, 'Evaluation of consecutive routine cases before and after the introduction of varenicline (N=412)' and appeared above a bar chart headed 'Abstinence rates at 4 weeks'. The bar chart compared the percentage abstinence rates of combination NRT (66.3%) with varenicline (72.1%). Between the bars appeared 'ns*'. It was stated that the bar chart was adapted from Stapleton *et al*. Two bullet points beneath the bar chart read '2 out of 3 smokers on combination NRT were abstinent at 4 weeks' and 'No statistically significant difference between combination NRT and varenicline*'. The two asterisks led the reader to a small footnote at the bottom of the slide, 'Evaluation not designed to detect a difference between combination NRT and varenicline'.

COMPLAINT

Pfizer noted that Stapleton *et al* discussed the short-term smoking cessation rates for varenicline, single NRT and combination NRT. The slide included the claim 'No statistically significant difference between combination NRT and varenicline'. While Stapleton *et al* '… observed little difference between the efficacy of varenicline and combination NRT therapy …' the authors also stated '… although this evaluation was not designed with adequate statistical power to test this'. Although a small footnote to this effect appeared at the bottom of the slide, the supplementary information to Clause 7 stated that 'In general, claims should not be qualified by the use of footnotes and the like'. Pfizer considered that overall the slide implied that there was no significant difference between varenicline and combination NRT smoking cessation therapies even though the authors explicitly stated that the study was not statistically powered to detect this. Johnson & Johnson argued that the observation of 'no statistically significant difference between NRT and varenicline' was acceptable as a standalone claim and presumably therefore did not require further clarification or qualification. Pfizer contested this assertion.

Pfizer further submitted that the slide clearly represented an attempt to mislead the audience as to the meaning of this result, otherwise why show it at all if the only thing to be demonstrated was that a study which was not designed or powered to show any difference did, indeed, fail to show any difference? Pfizer did not consider it was credible that this was the message that Johnson & Johnson wished to convey to its audience. It was clearly an attempt to lead the audience to believe that there was no difference in efficacy between varenicline and combination NRT treatment, something which this study was not designed to, and did not, demonstrate.

Pfizer was also concerned that the slide failed to mention that the aforementioned observation was not the primary endpoint of Stapleton *et al*. The authors stated that 'The results suggest that, with routine psychological and behavioural group support, varenicline is more effective than NRT in aiding short-term smoking cessation'. Due to this omission the slide did not fully and accurately reflect the authors' concluding views.

As a result, the slide was misleading regarding the design and results of the study and in particular the details of equivalent efficacy for combination NRT and varenicline in short-term smoking cessation. Pfizer alleged that the presentation was in breach of Clauses 7.2 and 7.8 of the Code and thus also Clause 9.1.

RESPONSE

Johnson & Johnson stated that the purpose of the presentation was to consider how treatment with high dose NRT could help health professionals, working in smoking cessation, achieve their challenging abstinence targets. Two key areas covered in the presentation were the established benefits of a high dose 16 hour patch compared with standard dose 16 hour patch (25mg vs 15mg) and the benefits of treatment with combination NRT vs monotherapy. Combination NRT usually involved the patient applying a patch to provide baseline nicotine levels and the use of an acute dosage form, as required, to relieve so called 'breakthrough' cravings. This method of treatment had been endorsed by the National Institute for health and Clinical Excellence (NICE), Action on Smoking and Health (ASH) and the Committee on Safety of Medicines (CHM).

The slide in question related to combination NRT usage. More specifically, the slide showed the

absolute 4 week abstinence rates, for varenicline and NRT combination therapy from Stapleton *et al*.

Stapleton *et al* compared the efficacy of varenicline and NRT in smoking cessation and evaluated the safety and efficacy of varenicline in people with mental illness. The study was conducted in an NHS tobacco dependence clinic in London and comprised an evaluation of cases before and after the introduction of varenicline. Patients receiving routine care (N=412) were included in the study and 4 week carbon monoxide verified abstinence rates were measured. The study also measured severity of withdrawal symptoms, incidence and severity of adverse drug symptoms, cost per patient treated and cost per successful quitter. In addition to abstinence rates for varenicline vs all NRT, the authors considered the comparative efficacy of varenicline vs single and combination NRT treatment.

The study demonstrated that cessation rates were higher with varenicline than all NRT (odds ratio = 1.70, 95% confidence interval = 1.09-2.67). However, the comparison between varenicline and combination NRT therapy showed '.... no evidence of a difference in success rates between varenicline and combination NRT (OR for CO-verified abstinence = 1.32, 95% CI=0.76-2.27 and OR for DH self-reported abstinence=1.38, 95% CI=0.76-2.52)'. In the discussion section of the paper, the authors stated '... this evaluation was not designed with adequate statistical power to test this'. The study was published in a peer reviewed journal.

Johnson & Johnson believed the results of Stapleton *et al* were of real importance to health professionals as this was the only published study which assessed the effect of combination NRT treatment in a 'real life' setting. It was also the only available study to have reviewed and compared the efficacy of varenicline and NRT combination treatment. Johnson & Johnson was of the strong view that this data provided those working in the field of smoking cessation with important and highly relevant information.

Both combination NRT therapy and varenicline were effective treatments for smoking cessation; both were commonly prescribed and therefore health professionals often had to decide which of the two to prescribe. The frequent use of combination NRT was illustrated in the study as 41% of patients who opted for NRT used a combination of more than one NRT product. Therefore, if choosing between these two treatments, it was important that the prescriber was aware of all relevant data. In order to help inform this decision, Johnson & Johnson submitted it was important to include the absolute efficacy rates for both treatments.

Johnson & Johnson took great care to ensure that the slide was not misleading in any way. The comparison between varenicline and NRT combination therapy was valid and had been made in the publication. Indeed, the slide simply reflected the comparison as presented by the authors. The bar chart was clearly presented and the bars annotated, in large font, with the absolute abstinence rates for the two groups. In fact the figures actually showed that the varenicline subjects achieved a numerically superior quit rate compared with those patients receiving combination NRT (72.1% vs 66.3% respectively). However, this difference was not statistically significant so the bar chart had been clearly labelled as 'ns'. The bullet point below the bar chart reinforced this fact.

It was entirely appropriate when presenting data in a bar chart to indicate whether or not there was a statistically significant difference between the treatments portrayed; not to do so risked giving a false impression. By providing both the raw data, as well as the statement in the chart and below the chart on the statistical significance, the prescriber was given all the relevant information on this comparison.

Johnson & Johnson strongly objected to Pfizer's allegation that it had attempted to mislead the audience as to the meaning of this result, '…otherwise why show it at all if the only thing to be demonstrated is that a study which was not designed or powered to show any difference did indeed fail to show any difference'. Johnson & Johnson acknowledged that absence of evidence was not the same as evidence of absence. However, it had taken great care to ensure that it had reflected accurately the absolute abstinence rates together with the statistical comparison conducted by the authors.

Johnson & Johnson's intention when developing this slide was to ensure that all relevant information was communicated unambiguously in order that prescribers could make an informed decision. The slide was headed 'Stapleton: Combination Success Rates at 4 weeks' and the bar chart provided the absolute quit rates from the study for both varenicline and combination NRT. These absolute quit rates on their own demonstrated that both combination NRT therapy and varenicline were effective treatments in smoking cessation, irrespective of any comparison between the two. This in itself was an important reason for presenting the data.

Although, as discussed in the publication, the study was not designed with adequate statistical power to detect a difference between combination NRT therapy and varenicline, the authors obviously felt this analysis to be of importance. Indeed, they conducted statistical tests to show that there was no evidence of a difference in success rates between varenicline and combination NRT (OR for CO-verified abstinence =1.32, 95%CI=0.76-2.27 and OR for DH self-report abstinence =1.38, 95% CI=0.76-2.52).

The slide was simply intended to reflect the authors' findings ie that no significant difference was detected between treatments. There was no attempt

to claim that combination NRT was superior or even equivalent to varenicline. The statement that the study did not detect a statistically significant difference between the treatments was absolutely true and could stand alone without further substantiation. However, to ensure absolute clarity regarding the nature of the data, Johnson & Johnson included the additional information about the statistical power of the study as a footnote. It would be inappropriate to use a footnote to correct a false impression. However, Johnson & Johnson did not believe that such an impression had been created. Johnson & Johnson was extremely careful to ensure that all relevant data had been presented in an accurate, balanced, fair, objective, and unambiguous way, based on an up-to-date evaluation of all the evidence. It had also been careful to ensure that all relevant information was reflected clearly. Johnson & Johnson did not believe that the footnote qualified the claim or corrected a wrong impression as suggested by Pfizer, but rather that it provided further useful information about the nature of the data. Johnson & Johnson noted that Pfizer had not provided any data to suggest that varenicline was superior in efficacy to combination NRT therapy.

In summary, Johnson & Johnson believed that the key messages communicated by the slide in question were that both varenicline and NRT combination therapy showed good overall efficacy and that Stapleton *et al* did not provide any evidence that varenicline and NRT combination therapy differed in terms of efficacy. The slide did not give a misleading impression that there was no difference in efficacy between varenicline and combination NRT. On the contrary, it faithfully presented the raw data from the study as well as the authors' conclusions on the comparison between varenicline and combination NRT therapy. The statement that there was 'no statistical difference between combination NRT and varenicline' made it clear that there was no evidence of a difference between treatments in this study, not that the treatments were equivalent. Johnson & Johnson believed that prescribers would understand this. In addition, this information was highly relevant as it was currently the only published data comparing varenicline and combination NRT.

Johnson & Johnson did not believe that the slide was misleading and therefore did not believe that it had breached Clause 7.2 as alleged.

In relation to the allegation that '... the slide failed to mention that the aforementioned observation was not the primary endpoint of Stapleton *et al*', Johnson & Johnson stated that the Code did not require that the primary efficacy endpoints of studies were always provided and it believed that it was acceptable to make comparisons using non-primary endpoints as long as the comparison was justified. In the context of a presentation on high dose NRT, there would be no sense in including the primary endpoint data relating to the comparison between mostly standard dose NRT and varenicline as that was not the subject of the presentation. Johnson & Johnson was not aware of any Code requirement to specify if data cited related to a secondary endpoint.

Johnson & Johnson noted Pfizer's allegation that due to this omission the slide did not fully and accurately reflect the concluding views of the authors. The authors made a number of other conclusions which, although no doubt of general interest, were not relevant to a presentation on NRT combination therapy. There was no obligation under the Code to reflect all the views of the authors of a study from which data was taken. However, the authors' conclusion relevant to combination NRT therapy was accurately reflected in the slide ie '… we observed little difference between the efficacy of varenicline and combination NRT therapy'.

It was entirely justified to present this data on combination NRT vs varenicline in the section of the presentation relating to combination NRT usage. Furthermore, there was no requirement under the Code to specify that the data presented was not the primary endpoint of the study.

Johnson & Johnson disagreed with Pfizer's assertion that the slide was in breach of Clause 7.8. Indeed the bar chart accurately presented the data from Stapleton *et al* and it was clear that it had been adapted from this study. Relevant details were included such as the patient numbers, nature of the cases and the frequency of the background support provided. The absolute quit rates for both varenicline and combination NRT were accurately represented and the quit rates were given within the bars. This allowed the prescriber to see clearly that the quit rates were numerically higher for varenicline. As the authors had conducted statistical significance testing, the fact that the comparison was not significant was reflected in the bar chart as 'ns'.

Johnson & Johnson believed the statement that there was no statistically significant difference between combination NRT and varenicline was acceptable as a standalone statement. However, to ensure that all relevant information was provided, it included a footnote explaining that the trial was not designed to detect a difference between treatments.

Based on the arguments above, Johnson & Johnson did not believe that it had breached Clauses 7.2 and 7.8.

Johnson & Johnson denied Pfizer's allegation that it had failed to maintain high standards. Johnson & Johnson believed that the presentation overall provided health professionals with useful and objective information on a fast developing area within smoking cessation. Moreover, the slide in question was based on robust data from a peer reviewed journal and was presented in a way as to ensure that prescribers had all relevant information to enable them to properly interpret the data.

Johnson & Johnson did not accept that the slide breached Clause 9.1.

PANEL RULING

The Panel noted that Stapleton *et al* compared the effectiveness of varenicline with NRT for smoking cessation and evaluated the safety and effectiveness of varenicline in people with mental illness. The authors stated that 'Varenicline was significantly more effective than single-product NRT therapy and increased cessation rates by about 14% … However, there was no evidence of a difference in success rates between varenicline and combination NRT'. In the discussion section the authors further stated 'The results suggest that, with routine psychological and behavioural group support, varenicline is more effective than NRT in aiding short-term smoking cessation' and 'Interestingly, we observed little difference between the efficacy of varenicline and combination NRT therapy, although this evaluation was not designed with adequate statistical power to test this'. The authors concluded that 'In this setting and with group support varenicline appears to improve success rates over those achieved with NRT …'.

The Panel noted that the slide in question was part of a presentation which examined high dose and combination NRT in hard to reach targets. The Panel noted Johnson & Johnson's submission that the data at issue was important and highly relevant to those working in smoking cessation. It was currently the only published data comparing varenicline and combination NRT. Nonetheless the presentation of such data had to comply with the Code. The information had to be sufficiently complete such as to allow clinicians to form their own opinion of the therapeutic value of the data presented.

In the Panel's view the design and content of the slide implied that Stapleton *et al* was powered to detect a difference between varencline and combination NRT and that was not so. The prominent heading 'Stapleton: Combination Success Rates at 4 weeks' introduced the comparison at issue and gave the impression that the study was adequately powered. Similarly the presentation of the data in the bar chart and the statement 'ns' reinforced the misleading impression that the study had sufficient power to compare varenicline with combination NRT.

The Panel noted that the supplementary information to Clause 7 stated, *inter alia*, 'In general claims should not be qualified by the use of footnotes and the like'. The footnote was insufficient to negate the misleading impression about the validity of the comparison and the power of the study. The slide was misleading in this regard as alleged. Breaches of Clauses 7.2 and 7.8 were ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that the presentation discussed high dose and combination NRT in hard to reach targets. The slide in question presented the combination NRT data vs varenicline. The Panel did not consider the slide in question misleading because it omitted reference to other outcomes from Stapleton *et al* as alleged. No breach of Clause 7.2 was ruled.

Complaint received **7 June 2010**

Case completed **22 July 2010**