CASE AUTH/2377/12/10

NOVO NORDISK v MERCK SHARP & DOHME

Promotion of Janumet

Novo Nordisk complained about one screen of an e-detail for Janumet (sitagliptin and metformin) produced by Merck Sharp & Dohme. The top of the screen featured a coloured band with the Janumet product logo in the top left hand corner. Below the band was the headline 'Powerful HbA_{1c} reductions helps more patients get to goal'. The screen depicted data showing the decrease in HbA_{1c} as reported by Raz *et al* (2008).

Novo Nordisk alleged that the heading contained a hanging comparison. 'More patients' compared to what? The clinical trial data compared sitagliptin (added to metformin) with placebo (added to metformin). Therefore the headline should state that the HbA_{1c} reduction induced by sitagliptin helped more people to achieve glycaemic target than the HbA_{1c} reduction achieved with placebo. Readers were likely to interpret the claim to mean that sitagliptin helped more patients to get to goal than other antihyperglycaemic treatments, which was not so. Thus the headline was misleading and could not be substantiated by the cited study, Raz *et al*.

Although the headline suggested that more patients got to goal, there was no mention of the proportion of patients who reached the target, nor was the goal itself clarified. A secondary endpoint in Raz *et al* was the proportion of patients who achieved the therapeutic goal of HbA_{1c} <7%. In context of the headline, the exact proportion of patients who got to goal was an essential piece of information. There was no doubt that a placebo-corrected 1% HbA_{1c} reduction looked more attractive than the observed rates of 22.1% (week 18) or 13.7% (week 30) which were the proportions of sitagliptin-treated patients who reached the <7% HbA_{1c} target. Putting this hidden 22.1/13.7% rates in the correct context, the readers should also have been informed that these rates were only numerically greater than the observed rate in the placebo arm. Raz *et al* suggested that there was no statistically significant difference between the two treatments in this regard. Novo Nordisk believed these were the reasons why Merck Sharp & Dohme did not report the actual outcome.

Novo Nordisk noted that the current type 2 diabetes clinical treatment recommendation from the National Institute for health and Clinical Excellence (NICE), set the target HbA_{1c} at 6.5% for the stage of diabetes which was investigated in Raz *et al* (second line oral anti-diabetic treatment). Since Raz *et al* had set the target HbA_{1c} as <7%, Novo Nordisk believed this must be clarified in the e-detail. The higher HbA_{1c} target defined in Raz *et al*, compared to the general UK recommendation, meant that the proportion of patients who achieved the UK relevant HbA_{1c} target of 6.5% would have been even smaller than the 22.1/13.7% reported in Raz *et al* in relation to the <7% target.

On the basis of the above, Novo Nordisk alleged that in the context in which it appeared, the headline was misleading and could not be substantiated.

Finally on the same screen, Novo Nordisk alleged that undue emphasis was placed on an HbA_{1c} drop of 1.8% in a subgroup of 20% (n=19) of patients from the sitagliptin group. Merck Sharp & Dohme had failed to highlight that this improvement was not statistically different from the HbA_{1c} drop observed in the placebo group, at least this was suggested by the authors who stated, 'Numerically greater HbA_{1c} reductions from baseline were observed in sitagliptin-treated patients with higher baseline HbA_{1c} values'.

The detailed response from Merck Sharp & Dohme is given below.

The Panel noted that Raz *et al* had evaluated the efficacy and safety of sitagliptin as an add-on to metformin therapy in patients with moderately severe type 2 diabetes (HbA_{1c} ≥ 8% and ≤11%). The primary efficacy endpoint was the reduction in HbA_{1c} at 30 weeks. The proportion of patients meeting the goal of HbA_{1c} <7% was also analysed.

The Panel considered that the headline 'Powerful HbA_{1c} reductions help more patients get to goal' was a claim for Januvia. The claim begged the question 'More patients than what?'. In that regard the Panel considered that the claim was a hanging comparison and as such it was not capable of substantiation. Breaches of the Code were ruled.

The Panel noted that no screen in the e-detail defined what the goal HbA_{1c} was. Raz *et al* had set a goal of < 7% although the NICE guidelines recommended a general target of ≤ 6.5% for patients on one glucose-lowering medicine. The Panel considered that with no numerical value of the goal in question, the material was not sufficiently complete such as to enable readers to form their own opinion of the therapeutic value of the medicine. In that regard the claim was misleading and could not be substantiated. Breaches of the Code were ruled.

The Panel noted that the study protocol pre-specified subgroups of patients according to baseline HbA_{1c}. Results showed that the higher a patient's baseline HbA_{1c}, the greater the fall in HbA_{1c} with sitagliptin therapy. In the subgroup with the highest baseline HbA_{1c} (≥ 10% n=20) the net

reduction in HbA_{1c} with sitagliptin therapy was 1.8% at week 18 and 1.4% at week 30. The smaller placebo-adjusted decrease at week 30 was due to a drop in HbA_{1c} in the placebo (metformin only) group, not a loss of glycaemic control in the sitagliptin group.

The Panel questioned whether the high baseline group was large enough for the results to be definitive. Merck Sharp & Dohme stated that a statistical analysis had not been undertaken but that in its view the reductions were clinically significant. Although the results appeared to support the view that the magnitude of the fall in HbA_{1c} from baseline was likely to be proportional to the baseline HbA_{1c}, the Panel did not consider that a definitive claim for a 1.8% reduction could be made based on the results from the small subgroup. The Panel further noted that the difference between placebo and sitagliptin narrowed at week 30 such that the difference between the two was only 1.4% (due to an improvement in the placebo group). Overall, the Panel considered that the 18 week results of the subgroup had been over emphasised. The figure of -1.8% appeared on a prominent downward pointing white arrow which was within a bright pink circle. The reader's eye would be drawn to the data which, in the Panel's view, was not based on a sufficiently robust dataset for such a claim. In that regard the Panel considered that the claim was misleading. Breaches of the Code were ruled which were appealed by Merck Sharp & Dohme.

The Appeal Board noted that Raz *et al* had assumed a within-group standard deviation of 1% for measuring HbA_{1c} and that approximately 86 patients per treatment group would provide 90% power to detect a true between-group difference of 0.5% in the mean change in HbA_{1c} from baseline.

The background colour of the e-detail screen at issue was mid blue and to the right of centre was a light blue box showing the placebo adjusted median change in HbA_{1c} from baseline when sitagliptin 100mg once daily was added to metformin therapy (n=95). A mid blue downward arrow showed a fall of 1% ($p<0.001$ vs placebo). To the right of the light blue box a prominent downward white arrow within a bright pink circle depicted a 1.8% placebo adjusted additional reduction in HbA_{1c} from baseline after 18 weeks in the subgroup of patients (n=19) with a baseline $HbA_{1c} \geq 10\%$.

The Appeal Board noted that both sets of data appeared prominently on the e-detail page but that only the results from the larger group had been subject to statistical analysis. Given the visual prominence of the downward white arrow, however, the Appeal Board considered that the reader would be drawn to the data from the high baseline group and would assume that it was as statistically robust as the data from the whole group, which was not so. The study was not powered to detect a difference in such a small group and in that regard the Appeal Board noted that the authors had stated that 'patients with higher baseline HbA_{1c} also *trended* towards larger reductions in HbA_{1c}' (emphasis added).

The Appeal Board considered that the results from the high baseline HbA_{1c} group had been over emphasised and in that regard the presentation of the data in the e-detail was misleading and did not accurately reflect Raz *et al*. The Appeal Board upheld the Panel's rulings of breaches of the Code. The appeal on this point was thus unsuccessful.

Novo Nordisk Limited complained about screen 7 of an e-detail (ref 02-11 JMT.10.GB.37010.AV) for Janumet (sitagliptin and metformin) produced by Merck Sharp & Dohme Limited. The top of the screen featured a coloured band with the Janumet product logo in the top left hand corner. Below the band was the headline 'Powerful HbA_{1c} reductions helps more patients get to goal'. The screen depicted data showing the decrease in HbA_{1c} as reported by Raz *et al* (2008). Novo Nordisk stated that inter-company dialogue had failed to resolve the matter. Merck Sharp & Dohme stated that the complaint was its first intimation that Novo Nordisk was dissatisfied with its response.

COMPLAINT

Novo Nordisk alleged that the heading contained a hanging comparison. 'More patients' compared to what? The clinical trial data detailed compared sitagliptin (added to metformin) with placebo (added to metformin). Therefore the headline should state that the HbA_{1c} reduction induced by sitagliptin helped more people to achieve glycaemic target than the HbA_{1c} reduction achieved with placebo which was correctly stated in the efficacy results part of the paper ('Compared to placebo, sitagliptin significantly increased the probability of achieving the HbA_{1c} goal of 7.0% …'). Since physicians relatively rarely treated patients with placebo, readers were likely to interpret the claim to mean that sitagliptin helped more patients to get to goal than other antihyperglycaemic treatments, which was not so. Thus the headline was misleading and could not be substantiated by the cited study, Raz *et al*, in breach of Clauses 7.2 and 7.4 of the Code.

Although the headline suggested that more patients got to goal, there was no mention on the screen about the proportion of patients who reached the target during the trial, nor was the goal itself clarified. A secondary efficacy endpoint in Raz *et al* was the proportion of patients who achieved the therapeutic goal of HbA_{1c} <7%. In context of the headline, the exact proportion of patients who got to goal was an essential piece of information for the readers. There was no doubt that a placebo-corrected 1% HbA_{1c} reduction looked more attractive for most clinicians than the observed rates of 22.1% (week 18) or 13.7% (week 30) which were the proportions of sitagliptin-treated patients who reached the <7% HbA_{1c} target. Putting this hidden 22.1/13.7% rates in the correct context, the readers should also have been informed that these

rates were only numerically greater than the observed rate in the placebo arm. This wording from Raz *et al* suggested that there was no statistically significant difference between the two treatments in this regard. Novo Nordisk believed these were the reasons why Merck Sharp & Dohme did not report the actual outcome to which it referred in the screen's headline.

Similarly, the therapeutic goal must have been defined since publication by the National Institute for health and Clinical Excellence (NICE) of the current type 2 diabetes clinical treatment recommendation, which was undoubtedly the most relevant UK clinical guideline and which set this target as 6.5% in general at the stage of diabetes which was investigated in Raz *et al* (second line oral anti-diabetic treatment). Since Raz *et al* had set the target HbA_{1c} as <7%, Novo Nordisk believed this must be clarified in the e-detail. The higher HbA_{1c} target defined in Raz *et al*, compared to the general UK recommendation, meant that the proportion of patients who achieved the UK relevant HbA_{1c} target of 6.5% would have been even smaller than the 22.1/13.7% which were reported in Raz *et al* in relation to the <7% target.

On the basis of the above, Novo Nordisk alleged that in the context in which it appeared, the headline was misleading in breach of Clause 7.2 and could not be substantiated, in breach of Clause 7.4.

Finally on the same screen, Novo Nordisk alleged that undue emphasis was placed on an HbA_{1c} drop of 1.8% in a subgroup of 19 patients from the sitagliptin group (only 20% of the sitagliptin patients). Merck Sharp & Dohme had failed to highlight that this improvement was not statistically different from the HbA_{1c} drop observed in the placebo group, at least this was suggested by the authors who stated, 'Numerically greater HbA_{1c} reductions from baseline were observed in sitagliptin-treated patients with higher baseline HbA_{1c} values'. Novo Nordisk alleged that the exaggeration of the statistically non-significant subgroup finding was in breach of Clauses 7.2 and 7.3.

RESPONSE

Merck Sharp & Dohme noted that on the screen in question, underneath the general headline 'Powerful HbA_{1c} reductions help more patients get to goal', details were given of the HbA_{1c} reductions seen when sitagliptin was added to metformin therapy vs placebo (Raz *et al*). No data were given on this screen (or on any other screen in the e-detail) about the relative proportions of patients achieving goal in Raz *et al*. Despite this, the complaint focused on the latter.

The two questions prompted by the first part of Novo Nordisk's complaint could be summarised as follows: Did the headline contain a hanging comparison within the meaning of the Code? And did the copy at least imply that a higher proportion of patients achieved treatment goal in the sitagliptin arm; and, if so, was this implication justified?

Concerning the headline, no specific product was mentioned. Merck Sharp & Dohme believed that the statement in question merely drew attention to the self-evident relationship between reductions in HbA_{1c} and attainment of goal a statement exemplified as far as sitagliptin was concerned by the data that followed. In effect, it stated that any agent that provided powerful HbA_{1c} reductions would be expected, almost by definition, to lead to an increased proportion of patients achieving goal, however defined. The remainder of the copy on the screen sought to answer the question as to whether sitagliptin provided such powerful HbA_{1c} reductions. As such, Merck Sharp & Dohme did not believe that the headline could possibly be interpreted as a hanging comparison within the meaning of the Code.

As noted above, the screen in question did not contain any data relating to the attainment of goal in Raz *et al*. Nevertheless, Merck Sharp & Dohme accepted that the headline could imply that sitagliptin led to a greater proportion of patients achieving goal in this study. Was that justified? Merck Sharp & Dohme maintained that it was. Raz *et al* contained the statement 'Compared with placebo, sitagliptin significantly increased the probability of achieving the HbA_{1c} goal of <7.0% at both week 18 and week 30 ($p=0.012$ and $p<0.001$, respectively)'. Thus, even if the copy had explicitly claimed an improvement in attainment of goal with sitagliptin, that claim would have been accurate and substantiated by Raz *et al*. Even in such a case, there was no obligation under the Code to include every detail of the data, provided that the claim was justified; Merck Sharp & Dohme stated that in any event no such explicit claim was made in the e-detail.

Merck Sharp & Dohme considered that Novo Nordisk's assertion that it was inadmissible to provide attainment-of-goal data vs placebo to be preposterous, and all the more so in that the data Novo Nordisk complained about were not included in the e-detail in the first place. Furthermore the phrase 'numerically greater', taken from Raz *et al* and cited in the complaint, referred to the increase in the number of patients achieving goal from week 18 to week 30 within the sitagliptin arm. It did not refer to the differences between the sitagliptin and placebo arms, which were indeed statistically significant, as evidenced by the quotation in the paragraph above. Finally, the target of 7% for HbA_{1c} goal was pre-specified in the trial protocol and was widely accepted as reasonable by the diabetological community.

Merck Sharp & Dohme did not accept that undue emphasis had been placed on the increased HbA_{1c} reduction in Raz *et al* in higher-baseline patients. Rather, the data was placed in context with the findings from the main part of the study. There was a well-recognised relationship between baseline HbA_{1c} and the magnitude of the HbA_{1c} reduction

with therapeutic agents (Bloomgarden *et al* 2006), and the higher-baseline data from Raz *et al* was thus relevant to potential prescribers. The subgroup analysis in Raz *et al* was pre-specified in the study protocol and as was usual in such analyses, no formal statistical analysis was done on the data, and Merck Sharp & Dohme did not suggest otherwise in the e-detail. Nevertheless, noted in inter-company correspondence - the reductions were clinically significant and the error bars in the graph in Figure 4 in Raz *et al* were widely separated. Finally, Merck Sharp & Dohme noted that it included all relevant data for this higher-baseline analysis in the e-detail, including placebo-adjusted figures, n-numbers and figures for both relevant time-points. It was difficult to see how it could have presented these data any more openly or transparently.

In conclusion, Merck Sharp & Dohme denied the alleged breaches of Clauses 7.2, 7.3 and 7.4.

In inter-company correspondence, Merck Sharp & Dohme stated that if the headline 'Powerful HbA_{1c} reductions help more patients get to goal' was interpreted as a claim for sitagliptin, it only stated that sitagliptin was effective, and that using it could be expected to lead to a greater proportion of patients reaching their treatment goal than would otherwise be the case. This was not equivalent to stating that sitagliptin was 'better' or 'stronger', which were true hanging comparisons. As such, Merck Sharp & Dohme believed that the headline was acceptable and its meaning was made abundantly clear by the context in which it appeared.

Merck Sharp & Dohme was also mystified by Novo Nordisk's assertion that the headline could be considered misleading. In Raz *et al* it was clearly stated that 'Compared with placebo, sitagliptin significantly increased the probability of achieving the HbA_{1c} goal of <7.0% at both week 18 and week 30 ($p=0.012$ and $p<0.001$, respectively)'. Given that the claim was therefore accurate and substantiable, Merck Sharp & Dohme did not understand how it could be considered misleading.

Merck Sharp & Dohme also did not accept the assertion that it was inappropriate or misleading to follow a claim that mentioned attainment of goal with absolute HbA_{1c} reduction data. As noted above, there was a self evident connection between the two, a connection that was made explicit in the headline to the screen in question. Furthermore, given that figures such as 7% were guidelines only, and that ideally treatment goals should be individualised to suit a patient's particular circumstances, it was as useful for potential prescribers to understand the absolute HbA_{1c} reductions that might be expected from an antidiabetic medicine as it was for them to know the proportions of patients attaining an HbA_{1c} goal.

It appeared that Novo Nordisk's concerns about the HbA_{1c} reductions in higher-baseline patients were based on a misinterpretation of Raz *et al*; the company appeared to believe that the 1.8% and 1.4% figures referred to non-placebo-adjusted and placebo-adjusted HbA_{1c} reductions in higher-baseline patients at the same time-point. This was not so as made clear in Figure 4 in the paper. Both figures were placebo-adjusted. The 1.8% figure was the reduction at week 18 and the 1.4% figure that at week 30. The pre-specified primary end-point of the trial was the HbA_{1c} reduction at week 18 and so 1.8% represented the 'official' result as far as higher-baseline patients were concerned. As noted in Raz *et al*, and in the e-detail, there was an improvement in HbA_{1c} in the placebo group from week 18, which resulted in a placebo-adjusted difference of 1.4% at week 30. In the interests of transparency, both figures were included in the e-detail.

Merck Sharp & Dohme did not understand why Novo Nordisk considered that these differences were not statistically significant as no formal statistical analysis was performed on the figures (as was normally the case with subgroup data of this nature). That said, the graphs in Figure 4 showed that the error bars for the sitagliptin and placebo reductions did not overlap by a considerable margin; in any event the reductions were undeniably clinically significant. The sentence from Raz *et al* quoted by Novo Nordisk referred to changes from baseline within the sitagliptin-treated group and not to differences with respect to placebo.

In summary, the sub-analysis of the higher-baseline patients was pre-specified in the study protocol, the HbA_{1c} reductions given in the e-detail were placebo-adjusted, figures were given for both relevant time-points and the text included both n-numbers and an explanation for the change in the differential reduction from week 18 to week 30. It was difficult to see how Merck Sharp & Dohme could have been any more open and transparent in representing these data.

Finally, Merck Sharp & Dohme noted that although 96 patients were randomised to receive sitagliptin, HbA_{1c} data were finally available for 95, as noted in Table 2 in Raz *et al*.

PANEL RULING

The Panel disagreed with Merck Sharp & Dohme's submission that the headline 'Powerful HbA_{1c} reductions help more patients get to goal' was a statement of the self-evident relationship between reductions in HbA_{1c} and attainment of goal and not a claim for sitagliptin. In the context of an e-detail for Januvia, and appearing beneath the product logo, the Panel considered that the headline would be read as a claim for that product.

The Panel noted that Raz *et al* had evaluated the efficacy and safety of sitagliptin as an add-on to metformin therapy in patients with moderately severe type 2 diabetes ($HbA_{1c} \geq 8\%$ and $\leq 11\%$). The primary efficacy endpoint was the reduction in HbA_{1c} at 30 weeks. The proportion of patients meeting the goal of HbA_{1c} <7% was also analysed.

The Panel considered that the headline 'Powerful HbA_{1c} reductions help more patients get to goal' was a claim for Januvia. The claim begged the question 'More patients than what?'. In that regard the Panel considered that the claim was a hanging comparison and as such it was not capable of substantiation. Breaches of Clauses 7.2 and 7.4 were ruled.

The Panel noted that neither the screen at issue nor any other screen in the e-detail defined what the goal HbA_{1c} was. Raz *et al* had set a goal of < 7% although the NICE guidelines recommended a general target of ≤ 6.5% for patients on one glucose-lowering medicine. The Panel considered that with no reference as to the numerical value of the goal in question, the material was not sufficiently complete such as to enable readers to form their own opinion of the therapeutic value of the medicine. In that regard the claim was misleading and a breach of Clause 7.2 was ruled. The Panel further considered that the claim could not be substantiated. A breach of Clause 7.4 was ruled.

The Panel noted that the study protocol pre-specified that subgroups of patients would be analysed for changes from baseline HbA_{1c} at weeks 18 and 30 to evaluate prescribing factors that could potentially influence treatment outcome. One of the subgroups was defined by baseline HbA_{1c} and results showed that the higher a patient's baseline HbA_{1c}, the greater the fall in HbA_{1c} with sitagliptin therapy. In the subgroup with the highest baseline HbA_{1c} (≥ 10% n=20) the net reduction in HbA_{1c} with sitagliptin therapy was 1.8% at week 18 and 1.4% at week 30. The smaller placebo-adjusted decrease at week 30 was due to a drop in HbA_{1c} in the placebo (metformin only) group, not a loss of glycaemic control in the sitagliptin group.

The Panel noted that according to Raz *et al* there were only 20 patients in the sitagliptin group (the e-detail stated 19 patients) with a baseline HbA_{1c} ≥ 10% and in that regard it questioned whether the group was large enough for the results to be definitive. Merck Sharp & Dohme stated that a statistical analysis had not been undertaken but that in its view the reductions were clinically significant. Although the results appeared to support the view that the magnitude of the fall in HbA1c from baseline was likely to be proportional to the baseline HbA_{1c}, the Panel did not consider that a definitive claim for a 1.8% reduction could be made based on the results from the small subgroup in Raz *et al*. The Panel further noted that the difference between placebo and sitagliptin narrowed at week 30 such that the difference between the two was only 1.4% (due to an improvement in the placebo group). Overall, the Panel considered that the 18 week results of the subgroup had been over emphasised. The figure of -1.8% appeared on a prominent downward pointing white arrow which was within a bright pink circle. The reader's eye would be drawn to the data which, in the Panel's view, was not based on a sufficiently robust dataset for such a claim. In that regard the Panel considered that the claim was misleading. Breaches of Clauses 7.2 and 7.3 were ruled which were appealed by Merck Sharp & Dohme.

APPEAL BY MERCK SHARP & DOHME

Merck Sharp & Dohme noted that Janumet was a fixed-dose combination of metformin and sitagliptin for the treatment of appropriate patients with type 2 diabetes. The screen in question presented data from Raz *et al*. In addition to text summarising the results of the study, the screen depicted in diagrams the mean reduction in HbA_{1c} of 1% obtained in the combination-treated group relative to placebo at 18 weeks (the scheduled end-point of the main trial) and the greater reduction of 1.8% seen in a high-baseline group (initial HbA_{1c} ≥10%), also at 18 weeks. Additional explanatory text, including further data, was appended to both diagrams.

Merck Sharp & Dohme submitted that the basis of Novo Nordisk's complaint about these data was that the results in the high-baseline group had been overemphasised, and the Panel upheld that view and ruled breaches of Clauses 7.2 and 7.3.

Merck Sharp & Dohme submitted that the Panel's ruling of a breach of Clause 7.3 was technically in error. The data in question fell outside the scope of this clause, which dealt specifically with comparisons with competitor products. The data presented in the e-detail were non-comparative. Accordingly, Merck Sharp & Dohme submitted that there was no case to answer with respect to this clause, and the remainder of its submission was focussed on the ruling of a breach of Clause 7.2. Merck Sharp & Dohme did not consider that the presentation of the high-baseline data was misleading.

Merck Sharp & Dohme noted that the Panel was concerned with the physical presentation of the high-baseline data (colour and prominence), and with the robustness of the data itself. As any judgement on whether data had been overemphasised depended largely on the robustness, significance and generalisability of the data in question, Merck Sharp & Dohme dealt with this issue first.

Merck Sharp & Dohme submitted that before addressing the specifics of the data presented in the e-detail, it might be helpful to consider their relevance. There was a widely recognised relationship between the level of baseline glycaemia and the glycaemic reductions obtained with antidiabetic agents. This relationship was investigated in a meta-analysis for 'traditional' antidiabetic agents by Bloomgarden *et al* (2006) and updated by two of the same authors for the DPP4-inhibitor class of drugs (of which sitagliptin was a member) in a letter in the New England Journal of Medicine (Bloomgarden and Inzucchi 2007). Further meta-analyses had been published by Chapell *et al* (2009), comparing sitagliptin with thiazolidinediones; and by Phung *et al* (2010), looking at all classes of oral antidiabetic agents.

Merck Sharp & Dohme submitted that it was clear from the evidence above that the average reductions in glycaemia reported in trials with antidiabetic agents only told part of the story of an individual agent's potential efficacy. It was therefore of great relevance for prescribers to have an accurate idea of the sort of glycaemic reductions they might expect to see in patients of often widely differing baseline glycaemic status.

Turning to the data presented in the Janumet e-detail, Merck Sharp & Dohme submitted that it might be useful to examine it using the criteria of Clause 7.2 of the Code as a guide. Were the data accurate? Merck Sharp & Dohme did not believe that there was any dispute that the high-baseline data presented in the e-detail was an accurate reflection of the findings from the Raz *et al*. As a minor point, the Panel suggested that there was a discrepancy between the n=19 figure cited in the e-detail and the n=20 figure for the high-baseline subgroup cited in the original paper. However, a footnote to a table of data in Raz *et al* clearly stated that the subgroup contributed only 19 patients to the full-analysis-set population.

Merck Sharp & Dohme noted that there was a question as to whether the data were balanced, bearing in mind the subsequent provision of the clause that 'Material must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine'. As previously stated Merck Sharp & Dohme submitted that it had included every relevant piece of information in the piece that would enable a potential prescriber to draw a conclusion as to the significance of the data presented. The nature of the subgroup was clearly identified, as was the n-number, the fact that this was a placebo-adjusted figure, and the population set. The Panel drew attention to the additional information presented concerning the results obtained at 30 weeks, showing that – as a result of an improvement in glycaemic status in the placebo group – the placebo-subtracted reduction in HbA_{1c} had fallen to 1.4%. The planned end-point of the study was at 18 weeks, and that, if anything, including the 30-week extension data in the piece further demonstrated Merck Sharp & Dohme's commitment to providing appropriately balanced information. The company noted that the absolute (as opposed to placebo-adjusted) reduction with sitagliptin in this high-baseline group remained virtually unchanged from 18 to 30 weeks.

With regard to the data being fair and objective, Merck Sharp & Dohme submitted that at several points in its ruling, the Panel expressed concern that an n-number of 19 might not be considered large enough for the results to be definitive. Leaving aside the existence of additional supportive data obtained with sitagliptin (see below), it should be noted, firstly, that the figure of n=19 referred only to the number of patients in the high-baseline subgroup treated with active product. There were a further 13 patients in the high-baseline subgroup treated with placebo, giving a total n of 32 for the subgroup as a whole. It was this figure that was relevant in assessing the validity of a placebo-adjusted comparison. Raz *et al* demonstrated that, at both 18 and 30 weeks, there was very wide separation between the confidence intervals of the placebo- and sitagliptin-treated groups for all levels of baseline glycaemia, and particularly so for the baseline subgroup of 10% or above. This strongly suggested that the patient numbers involved were more than sufficient to demonstrate a significant difference between the two treatment groups.

Merck Sharp & Dohme also noted that, in assessing fairness and emphasis, the data related to the primary indication for which Janumet was licensed, ie improvement in glycaemia. Furthermore, the analysis of the high-baseline subgroup was not carried out post hoc, but was a pre-specified analysis in the study protocol.

Merck Sharp & Dohme noted that there was a question as to whether the data were 'based on an up-to-date evaluation of all the evidence' and did they 'reflect that evidence clearly'? Merck Sharp & Dohme submitted that the data from Raz *et al* about glycaemic reductions in higher-baseline patients was not an isolated clinical finding. On the contrary – in addition to the evidence from the meta-analyses referred to above – several individual clinical trials with sitagliptin had demonstrated the same differential reductions in HbA_{1c} relative to baseline, and of broadly the same extent as shown in Raz *et al*. For example:

- Nauck *et al* (2007): A 52-week trial which compared the effects of sitagliptin with a sulphonylurea (glipizide), both on a background of metformin. For both active treatments, there was a clear progression in the HbA_{1c} reduction with increasing HbA_{1c} baseline. At the highest baseline subgroup examined ($HbA_{1c} \geq 9\%$, ie slightly lower than in Raz *et al*), the reductions in the sitagliptin (n=21) and glipizide (n=33) arms were 1.68% and 1.76%, respectively.

- Aschner *et al* (2010): A 24-week study which compared sitagliptin monotherapy with metformin monotherapy. As the overall mean HbA_{1c} baseline in the study was only just over 7%, the highest baseline subgroup examined was again somewhat lower than the highest group in Raz *et al* (≥8%), but a proportionally similar result was obtained, with reductions in the sitagliptin (n=74) and metformin (n=73) arms of 1.1% and 1.2% respectively.

- Williams-Herman *et al* (2009): A 54-week trial which looked at the effects of initial therapy with sitagliptin and metformin, both separately and in combination. The highest baseline subgroup examined in this study was equivalent to that investigated in Raz *et al* (≥ 10%). The reduction in this subgroup in the sitagliptin-only arm was approximately 1.8%, and was even more marked in the patients treated with initial combination therapy (over 3% in the high-dose combination arm).

In summary Merck Sharp & Dohme submitted that the high-baseline data in the e-detail related to the primary licensed indication for the medicine. The relevant analysis was pre-specified in the study protocol and the data presented accurately reflected the findings of the study.

Every piece of information that would help a physician form an opinion as to the validity and significance of the data was included in the piece. The widely separated confidence intervals demonstrated that the numbers involved were great enough to show an effectively significant difference between the two treatment arms. Merck Sharp & Dohme submitted that the data exemplified a recognised phenomenon seen with all antidiabetic agents; and one, moreover, of great relevance to potential prescribers

The data formed part of a larger body of evidence from multiple randomised controlled trials, all of which demonstrated the same effect to proportionally the same extent.

Given the above, Merck Sharp & Dohme submitted that the information would have to be presented in a very unbalanced manner indeed to render it actively misleading.

As far as presentation was concerned, pink was not chosen for the background colour with any sinister intent; it was one of the standard Januvia livery colours and since launch had been used for a variety of design elements (headings, illustrations, backgrounds, etc). If the Panel was correct that the eye was drawn to the colour to some extent, this was surely not to the total exclusion of everything else on the page. Merck Sharp & Dohme noted that the heading and much of the text in the box showing the main trial results were also in pink. Given the natural tendency to read from left to right, the high-baseline data in the e-detail would be seen as intended: as adjunctive and supplementary information to the main results of study.

Taken in conjunction with the additional textual information supplied, Merck Sharp & Dohme submitted that a downward-pointing arrow was not an unreasonable way to represent the essentials of the data.

Merck Sharp & Dohme finally noted that when it presented the same data in the Januvia detail aid, the main results from the trial were presented in a box well over twice as wide as the circle containing the high-baseline data. While this was not possible for an electronically formatted piece, the main-results box still occupied a significantly greater area than the pink circle.

COMMENTS FROM NOVO NORDISK

Novo Nordisk fully agreed with Merck Sharp & Dohme that the relationship between baseline glycaemic control and subsequent glycaemic reduction with any antidiabetic agent was widely recognised. This was probably the reason why Raz *et al* aimed for a trial population with higher baseline HbA_{1c} than the average baseline HbA_{1c} levels in previous sitagliptin trials, as was reflected in the introduction 'Hence, the purpose of the present 30-week study was to provide additional experience with the combination therapy of sitagliptin and metformin, including experience in patients with a different range of baseline HbA_{1c} (8.0-11.0%) than was examined in these prior studies of sitagliptin as an add-on to metformin monotherapy'. Thus the trial itself with its full trial population had been designed to show a potentially larger HbA_{1c} reduction than what was observed in the previous sitagliptin trials. Therefore Novo Nordisk failed to understand Merck Sharp & Dohme's explanation that the average reductions in glycaemia reported in trials with antidiabetic agents only told part of the story of an individual agent's potential efficacy, in context with Raz *et al*. Novo Nordisk alleged that the reason to highlight the average reduction of HbA_{1c} in a small subset of patients was to overemphasise the 1.8% reduction in context with the heading of the page which promised that more patients get to goal with Janumet.

In terms of the relevance of highlighting the glycaemic results from such a subgroup, Novo Nordisk noted that the most widely recognised and followed UK clinical guideline, the NICE clinical recommendation in type 2 diabetes, suggested a general HbA_{1c} target of 6.5% with the first (OAD monotherapy) or second-line therapies (dual OAD combination). Raz *et al* reflected the latter situation (adding a second-line OAD after metformin monotherapy failure). This meant that the GP, the target audience of this promotional material, would usually consider sitagliptin as an add-on option at much lower HbA_{1c} levels than the baseline glycaemic control in the small subgroup was. Therefore, Novo Nordisk disagreed that the subgroup of patients with an average HbA_{1c} level of 10.5% would be of clinical relevance.

Novo Nordisk fully acknowledged that clinical reality could be different than the ideal treatment scenarios in the different guidelines. However even in the case of the representative UK primary care database analyses conducted and published by Calvert *et al* (2007), the average HbA_{1c} level when the second-line OAD therapy was added was 9.04% which was fairly comparable with the average baseline HbA_{1c} level of the patients in Raz *et al* (9.1%). Thus Novo Nordisk strongly believed that the emphasis on the subgroup in the material was undue, unnecessary and irrelevant from clinical perspective.

Novo Nordisk agreed with the Panel which questioned the robustness of any results from a subgroup of 19 patients even if the subgroup analysis was pre-specified in the trial protocol. Novo Nordisk clearly disagreed with Merck Sharp & Dohme's explanation that the additional 13 patients in the placebo arm would increase the robustness of the observation within the sitagliptin group. The results from a subgroup analysis could only be used

in the way Merck Sharp & Dohme used the HbA_{1c} reduction in the small subset of patients (namely placing the same emphasis on the result from the overall study cohort as on the results from the subgroup) if the robustness of such finding was substantiated by proving a statistically significant difference between the active and placebo arms with an appropriate statistical test. If no such test had been conducted (which was the case here), the difference could be merely driven by chance. Hence it was inappropriate to emphasise it in any way in a piece of promotional material unless it was clearly stated that no statistical comparison had been conducted.

On the basis of the above, Novo Nordisk upheld its position regarding the subgroup results in the material in question and agreed with the Panel's ruling of a breach of Clauses 7.2 and 7.3.

APPEAL BOARD RULING

The Appeal Board noted that the e-detail page at issue featured results taken from Raz *et al*. The authors had assumed a within-group standard deviation of 1% for measuring HbA_{1c} and that approximately 86 patients per treatment group would provide 90% power to detect a true between-group difference of 0.5% in the mean change in HbA_{1c} from baseline.

The background colour of the e-detail page at issue was mid blue and to the right of centre was a light blue box showing the placebo adjusted median change in HbA_{1c} from baseline when sitagliptin 100mg once daily was added to metformin therapy (n=95). A mid blue downward arrow showed a fall of 1% ($p<0.001$ vs placebo). To the right of the light blue box a prominent downward white arrow within a bright pink circle depicted a 1.8% placebo adjusted additional reduction in HbA_{1c} from baseline after 18 weeks in the subgroup of patients (n=19) with a baseline HbA_{1c} ≥10%.

The Appeal Board noted that both sets of data appeared prominently on the e-detail page but that only the results from the larger group had been subject to statistical analysis. Given the visual prominence of the downward white arrow, however, the Appeal Board considered that the reader would be drawn to the data from the high baseline group and would assume that it was as statistically robust as the data from the whole group, which was not so. The study was not powered to detect a difference in such a small group and in that regard the Appeal Board noted that the authors had stated that 'patients with higher baseline HbA1c also *trended* towards larger reductions in HbA_{1c}' (emphasis added).

The Appeal Board considered that the results from the high baseline HbA_{1c} group had been over emphasised and in that regard the presentation of the data in the e-detail was misleading and did not accurately reflect Raz *et al*. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was thus unsuccessful.

The Appeal Board noted Merck Sharp & Dohme's submission that the Panel's ruling of a breach of Clause 7.3 was technically in error because that clause dealt specifically with comparisons with competitor products. The Appeal Board however disagreed, Clause 7.3 dealt with comparisons generally. The Appeal Board noted that the data was derived from a parallel-group study in which sitagliptin or placebo was added to ongoing metformin therapy. The study thus compared sitagliptin/metformin combination therapy with metformin monotherapy. The Appeal Board noted its comments above and upheld the Panel's ruling of a breach of Clause 7.3. The appeal on this point was thus unsuccessful.

Complaint received **23 December 2010**

Case completed **5 April 2011**