CASE AUTH/2938/2/17

SANOFI v NOVO NORDISK

Tresiba leavepiece

Sanofi UK complained about a Tresiba (insulin degludec) leavepiece (ref UK/TB/1214/0302(4)) issued by Novo Nordisk Ltd. Tresiba was for the treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year.

The claim 'Tresiba provides 75% less variability in glucose-lowering effect over 24 hours versus insulin glargine U100' appeared as a heading to page 3 above a bar chart titled 'Within-patient variation in glucose-lowering effect over 24 hours, calculated at two-hourly intervals in patients with type 1 diabetes'. A bold and prominent claim adjacent to the bar chart read '75% Less Variability'. Text beneath discussed within-patient day-to-day variability and the benefits of lower variability. These being 'A potentially lower risk of hypo- and hyperglycaemia' and 'Potentially aids titration to glycaemia targets'.

Sanofi stated that this page did not clearly indicate that the information provided related specifically to a pharmacodynamic clamp study. The only indirect reference to a clamp study was along the small font sized title alongside the Y axis of the bar chart. Hence the claim 'Tresiba provided 75% less variability in glucose lowering effect over 24 hours vs insulin glargin U100' was misleading without sufficient qualification that this related to the results from an experimental clamp study as it strongly suggested that the outcomes shown related to real life clinical practice which had yet to be proven with clinical studies.

Sanofi stated that, in addition, the disproportionate very large font size used on the page for '75% Less Variability' compared with the font size used beneath it distorted the perceived impact of such outcomes derived from the clamp study. Sanofi noted that the page at issue also included claims of the potential clinical benefits of lower variability based on the results of the clamp study and alleged that the claims 'A potentially lower risk of hypo- and hyperglycaemia' and 'Potentially aids titration to glycaemic targets' were misleading and not fully substantiated by Heise *et al*.

The detailed response from Novo Nordisk appears below.

The Panel noted that Heise *et al* stated that 'a limitation of this study was the difficulty in transferring the results from an experimental clamp setting to clinical reality. As noted, clinical studies show a lower rate in (nocturnal) hypoglycaemia with [Tresiba] compared with [insulin glargine] but it is not possible to attribute this clinical difference solely to the difference in variability between the two insulins'. The authors concluded that the results showed that, at steady state, Tresiba had a significantly more predictable glucose-lowering effect from day-to-day compared to insulin glargine.

The Panel noted that the front page of the leavepiece featured clinical claims for Tresiba and referred to a lower risk of nocturnal hypoglycaemia vs insulin glargine U100. The second page introduced three patients that might be suitable for treatment. Page 4 presented nocturnal hypoglycaemia data, Bode *et al*, which compared Tresiba and insulin glargine U100 and highlighted a significantly lower risk of nocturnal hypoglycaemic events with Tresiba. The gate-folded design of the leavepiece was such that the page in question, page 3, could only be viewed when the leavepiece was fully open such that it was the central page in a triple page spread to be read alongside pages 2 and 4 and was an integral part of the clinical story presented across the triple page spread.

The Panel noted Novo Nordisk's submission that the informed audience would understand that there was no way to assess the variability and pharmacodynamic properties of insulins other than by a euglycaemic clamp study. The Panel noted Novo Nordisk's submission regarding the reference in the SPC to the lower day-to-day variability of the glucose-lowering action of Tresiba. The Panel also noted Novo Nordisk's submission that the labelling of the Y axis of the bar chart which stated 'Day-to-day variability (coefficient of variation (CV*) %) Area under the glucose infusion rate (GIR) curve' showed that the data was from a clamp study. The Panel noted that page 3 had to be turned to read the labelling which was in a small typeface and in its view was not sufficiently prominent. This was especially so given the design of the page which drew the reader's eye to other highlighted text. The Panel accepted that part of the audience might be well-informed and thus aware that variability of glucose lowering response was assessed using euglycaemic clamp studies. Some might be aware of the nature of the data but not aware of the study authors' caveats regarding its clinical application. The immediate impression was of paramount importance.

In the particular circumstances of this case the Panel considered that given the caveats in Heise *et al* and the presentation of the data as an integral part of a clinical story leading inexorably to those clinical benefits (lower risk of nocturnal hypoglycaemia) outlined, *inter alia*, on page 4 it should have been made clearer that the data on page 3 derived from a clamp study and that a degree of caution ought to be exercised in the application of the results to the clinical situation. The Y axis labelling was insufficient in this regard. On balance the Panel considered that the failure to do so implied that the data derived from Heise *et al* had definitive clinical benefit and so meant that the page was misleading in this regard. Breaches of the Code were ruled.

The Panel noted its comments above about Heise *et al* and the study's limitations and the impression created by the page in question. The Panel considered that within the context of the page in question the claim of benefits of lower variability would be seen as a claim for Tresiba as would the two bullet points, 'A potentially lower risk of hypo- and glycaemic attacks' and 'Potentially aids titration to glycaemic targets' which were misleading. A breach of the Code was ruled.

The Panel noted that the safety section of Heise *et al* stated that 'In total 100 confirmed hypoglycaemic episodes were observed with [Tresiba] compared with 95 episodes with [insulin glargine]' and 'fewer confirmed nocturnal hypoglycaemic episodes were reported for [Tresiba] (16 episodes in 9 subjects) than iGlar (26 episodes in 13 subjects)' and that 'The observed number of hypoglycaemic episodes might be artificially high due to the fixed dosing level of 0.4U/kg of [Tresiba] and [insulin glargine]'. The Panel noted its

comments above about the misleading impression given by the page including the two bullet points in question. The Panel did not consider that the primary impression given by the bullet points in question could be substantiated by Heise *et al* as alleged and a breach was ruled.

Sanofi alleged that the claim '142 Fewer Nocturnal Hypoglycaemic Events' on page 4 was misleading and exaggerated the effect of Tresiba vs glargine U100. The very large font size and undue emphasis of the large sized number in contrast to the much smaller font size used below 'for every 100 patients ...' was misleading and exaggerated the reported hypoglycaemic event difference between the two insulins. There was no significant difference in the rate of confirmed overall hypoglycaemic episodes for Tresiba vs insulin glargine U100 in patients with type 1 diabetes as detailed in the small font sized statement at the bottom right-hand side of the page at issue.

The Panel noted that the bold and prominent claim in question '142 Fewer Nocturnal Hypoglycaemic Events' appeared adjacent to the graph and in the same green font as the prominent page heading. The qualification 'for every 100 patients treated with Tresiba per year versus insulin glargine U100' appeared in much smaller black font, as a distinct and separate paragraph below and did not immediately appear to be part of the claim in question. This was compounded by the fact that the font colour and prominence of the claim in question and the page heading visually linked the two drawing the reader's eye away from the qualification to the claim in question. In the Panel's view it would not be immediately obvious that the separate paragraph beneath was in fact a continuation of the claim above and formed part of the same sentence.

The Panel noted that the statement that there was 'no significant difference in the rate of confirmed overall hypoglycaemic episodes for Tresiba versus insulin glargine U100 in patients with type 1 diabetes (p=ns)' was the third paragraph below the claim in question again in black smaller font.

The Panel considered that the claim '142 Fewer Nocturnal Hypoglycaemic Events' exaggerated the reported hypoglycaemic event difference between the two insulins. The Panel disagreed with Novo Nordisk's submission that the statement regarding no significant difference in the rate of confirmed hypoglycaemic episodes was sufficiently prominent and considered that it did not negate the overall impression of the page. Nor in the Panel's view and for the reasons stated above was the claim in question suitably qualified by the paragraph immediately beneath. The Panel considered that the comparison was misleading in that regard and potentially exaggerated the effect of Tresiba and a breach of the Code was ruled.

Sanofi UK complained about a Tresiba (insulin degludec) leavepiece (ref UK/TB/1214/0302(4)) issued by Novo Nordisk Ltd. Tresiba was for the treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year.

Novo Nordisk submitted that the aim of the leavepiece was to provide information about the pharmacodynamic variability of Tresiba vs insulin glargine U100 which was reflected in Bode *et al* (2013), a large scale clinical trial. The leavepiece also provided details relating to the two available Tresiba preparations and dosing, and suggested some patient types for which Tresiba might be suitable.

The front page referred to the duration of action, reductions in HbA_{1c} and price reductions. It also claimed that Tresiba had a lower risk of nocturnal hypoglycaemia vs insulin glargine U100 referenced to Rodbard *et al* (2013) and Bode *et al*.

1 Claim 'Tresiba provides 75% less variability in glucose-lowering effect over 24 hours versus insulin glargine U100'

This claim appeared as a heading to page 3 above a bar chart titled 'Within-patient variation in glucose-lowering effect over 24 hours, calculated at two-hourly intervals in patients with type 1 diabetes'. A bold and prominent claim adjacent to the bar chart read '75% Less Variability'. Text beneath discussed within-patient day-to-day variability and the benefits of lower variability. These being 'A potentially lower risk of hypo- and hyperglycaemia' and 'Potentially aids titration to glycaemia targets'. Claims and data on the page were referenced to Heise *et al* (2012).

COMPLAINT

Sanofi stated that this page illustrated the outcomes of a comparative pharmacodynamic euglycaemic glucose clamp study between Tresiba and insulin glargine U100, manufactured by Sanofi (Heise *et al*). The clamp study was conducted to assess day-to-day variability in glucose-lowering effect in 54 subjects with type 1 diabetes. Clamp studies were commonly conducted to assess the pharmacodynamic properties of insulins to measure parameters such as the duration of action and variability of glucose lowering response in an artificial experimental environment. As outlined by Heise *et al*, 'Care needs to be taken when extrapolating results from experimental situations to clinical practice'. In addition, the discussion stated that 'A limitation of this study is the difficulty in transferring the results from an experimental clamp setting to clinical reality. As noted, clinical studies show a lower rate in (nocturnal) hypoglycaemia with [Tresiba] compared with [insulin glargine], but it is not possible to attribute this clinical difference solely to the difference in variability between the two insulins'.

Sanofi stated that page 3 of the leavepiece did not clearly indicate to the reader that the information provided related specifically to a pharmacodynamic clamp study. There was no mention in the title of the page that the information was derived from such an experimental clamp study. The only indirect reference to a clamp study was along the small font sized title alongside the Y axis of the bar chart. Hence the claim 'Tresiba provided 75% less variability in glucose lowering effect over 24 hours vs insulin glargin U100' was misleading without sufficient qualification that this related to the results from an experimental clamp study. Without sufficient and prominent qualification, the claim strongly suggested that the outcomes shown related to real life clinical practice which had yet to be proven with robust clinical studies. Sanofi believed that particular care was needed when making claims in promotional material based upon an experimental pharmacodynamic clamp study, particularly when its main author indicated that caution was required in extrapolating such data to a real clinical setting. Sanofi alleged that the claim was misleading in breach of Clauses 7.2 and 7.3.

Sanofi stated that, in addition, the disproportionate very large font size used on the page to illustrate '75% Less Variability' compared with the font size used beneath this statement distorted the perceived impact of such outcomes derived from the clamp study. Such distortion created the impression that less 'within-patient variability' would have definitive clinical benefit relevant for Tresiba vs insulin glargine U100. This was not the case as the outcomes from such an experimental clamp study could not be made definitively generalisable to a real life clinical

setting due to the experimental nature of pharmacodynamic euglycaemic clamp studies. Sanofi alleged breaches of Clauses 7.2 and 7.8.

Sanofi noted that the page at issue also included claims of the potential clinical benefits of lower variability based on the results of the clamp study. Sanofi believed that the claims 'A potentially lower risk of hypo- and hyperglycaemia' and 'Potentially aids titration to glycaemic targets' were misleading and not fully substantiated by Heise *et al*. The reported study safety outcomes indicated that 'In total, 100 confirmed hypoglycaemic episodes observed with iDeg (Tresiba) compared with 95 episodes with iGlar. Fewer confirmed nocturnal hypoglycaemic episodes were reported for iDeg (16 episodes in 9 subjects) than iGlar (26 episodes in 13 subjects). The observed number of hypoglycaemic episodes might be artificially high due to the fixed dosing level of 0.4U/kg of iDeg and iGlar'.

Sanofi alleged that claims relating to the potential benefits of lower variability were misleading and could not be substantiated in breach of Clauses 7.2 and 7.4.

RESPONSE

Novo Nordisk agreed that euglycaemic clamp studies were conducted to assess the pharmacodynamic properties of insulins to measure parameters such as variability of glucose lowering response. These studies had been conducted since 1979 and were regarded as the gold standard for investigation of insulins by agencies such as the European Medicines Agency (EMA). In its guidance for clinical investigation for medicinal products for the treatment of type 2 diabetes, the EMA Committee for Proprietary Medicinal Products (CPMP) stated 'data on time-action profiles using the euglycaemic clamp technique should be available, providing data based on the glucose infusion rate'. Novo Nordisk submitted that for an informed audience, such as would be reading a promotional leavepiece for a diabetes treatment, it would be understood that there was no other way to assess the variability and pharmacodynamic properties of insulins.

Novo Nordisk submitted that the claim, '75% Less Variability' was supported by the bar chart. The Y-axis of the chart clearly stated 'Area under the glucose infusion rate (GIR) curve' which showed that it was from a clamp-study. The claim of '75% Less Variability' was quantified and substantiated based on the results of Heise *et al* and therefore was not misleading. Novo Nordisk thus denied breaches of Clauses 7.2 and 7.3.

Novo Nordisk further submitted that Section 5.1 of the Tresiba summary of product characteristics (SPC) also substantiated the lower day-to-day variability of the glucose-lowering action of insulin degludec:

> 'The insulin degludec glucose-lowering action at steady state shows four times lower day-to-day variability in terms of Coefficients of Variation (CV) for the glucose-lowering effect during 0-24 hours (AUC GIR, SS) and 2–24 hours (AUC GIR2-24h, SS) as compared to insulin glargine.'

Therefore the claim was further substantiated.

Novo Nordisk stated that the font size used for the claim '75% Less Variability' was reasonable and not disproportionate to the size of the chart which illustrated this difference. The statements below the claim regarding potential clinical benefits were not in the same font size and therefore

did not create the impression that less within-patient variability would have 'definitive clinical benefit ...' as alleged. Novo Nordisk submitted that the requirements of Clauses 7.2 and 7.8 had been met.

With reference to the benefits of lower variability, both claims stated the potential of lower variability, not definitive effects. Heise *et al* stated:

> 'The difference in within-subject variability is expected to be of clinical relevance and to have an impact upon the risk of both hyper- and hypoglycaemia for the individual patient .... Although caution should be taken when extrapolating from experimental situation to clinical practice, it is worth noting that the predicted hypoglycaemia risks are qualitatively consistent with the results of clinical trials ….'

and

> 'A lower variability of effect would be a major advantage when titrating the individual insulin dose and might provide a mechanistic explanation of the differences in the hypoglycaemic incidence observed in the clinical trials.'

The clinical relevance of less variability had also been documented in other publications including Bekker *et al* (2015) a Sanofi supported paper which stated:

> 'low diurnal fluctuation in insulin exposure was expected to be of clinical relevance by reducing an individual's risk of hyperglycaemia and hypoglycaemia'

and

> 'In a clinical setting, high reproducibility would be a major advantage when titrating an individual's insulin dose, owing to a more predictable insulin exposure'.

Novo Nordisk thus submitted that the claims made about the potential benefits of lower variability could be supported by Heise *et al* and other published studies. The company denied any breaches of Clauses 7.2 and 7.4.

PANEL RULING

The Panel noted that it was an established principle under the Code that all claims related to the clinical situation unless otherwise stated. The supplementary information to Clause 7.2 stated that care must be taken with the use of data derived from *in vitro* studies and the like so as to not mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance.

The Panel noted that the entire page at issue (page 3) was referenced to Heise *et al* which in the discussion section stated that 'a limitation of this study was the difficulty in transferring the results from an experimental clamp setting to clinical reality. As noted, clinical studies show a lower rate in (nocturnal) hypoglycaemia with [Tresiba] compared with [insulin glargine] but it is not possible to attribute this clinical difference solely to the difference in variability between the two insulins'. The authors concluded that the results showed that, at steady state, Tresiba had a significantly more predictable glucose-lowering effect from day-to-day compared to insulin glargine.

The Panel noted that the front page of the leavepiece featured clinical claims for Tresiba and referred to a lower risk of nocturnal hypoglycaemia vs insulin glargine U100. The second page introduced three patients that might be suitable for treatment. One patient had a fear of nocturnal hypoglycaemia, another found it hard to keep to a strict treatment regimen and the third found it difficult to take twice daily doses of insulin. Directly after the third page (the page at issue) page 4 presented nocturnal hypoglycaemia data from a randomised control trial, Bode *et al*, which compared Tresiba and insulin glargine U100 and highlighted a significantly lower risk of nocturnal hypoglycaemic events with Tresiba. The gate-folded design of the leavepiece was such that the page in question, page 3 could only be viewed when the leavepiece was fully open such that it was the central page in a triple page spread to be read alongside pages 2 and 4. Whilst page 3 had to be capable of standing alone in relation to the requirements of the Code, context was relevant. The Panel considered that the design of the leavepiece was such that the page in question was an integral part of the clinical story presented across the triple page spread.

The Panel noted Novo Nordisk's submission that the informed audience would understand that there was no way to assess the variability and pharmacodynamic properties of insulins other than by a euglycaemic clamp study. The Panel noted Novo Nordisk's submission regarding the reference in the SPC to the lower day-to-day variability of the glucose-lowering action of Tresiba. The Panel also noted Novo Nordisk's submission that the labelling of the Y axis of the bar chart which stated 'Day-to-day variability (coefficient of variation (CV*) %) Area under the glucose infusion rate (GIR) curve' showed that the data was from a clamp study. The Panel noted that page 3 had to be turned to read the labelling which was in a small typeface and in its view was not sufficiently prominent. This was especially so given the design of the page which drew the reader's eye to other highlighted text. The Panel accepted that part of the audience might be well-informed and thus aware that variability of glucose lowering response was assessed using euglycaemic clamp studies. Some might be aware of the nature of the data but not aware of the study authors' caveats regarding its clinical application. The immediate impression was of paramount importance particularly for those that might not study it in detail.

The Panel considered that whether the presentation of data derived from a clamp study was acceptable under the Code in relation to implied clinical benefit depended on the individual circumstances of each case: the nature of the material, the potential extrapolation to the clinical situation and the audience would be relevant. The Panel noted the caveats in the study in question as set out above. The Panel also noted the strong visual link between the prominent claim '75% Less Variability' on the page in question and the prominent clinical claims on page 4. The Panel noted that page 3 did not state that Heise *et al* used a fixed dose of 0.4U/kg. In the particular circumstances of this case the Panel considered that given the caveats in Heise *et al* and the presentation of the data as an integral part of a clinical story leading inexorably to those clinical benefits (lower risk of nocturnal hypoglycaemia) outlined, *inter alia*, on page 4 it should have been made clearer that the data on page 3 derived from a clamp study and that a degree of caution ought to be exercised in the application of the results to the clinical situation. The Y axis labelling was insufficient in this regard. On balance the Panel considered that the failure to do so implied that the data derived from Heise *et al* had definitive clinical benefit and so meant that the page was misleading in this regard. Breaches of Clauses 7.2 and 7.3 were ruled.

The Panel further noted Sanofi's allegation that the disproportionate large font size of the claim '75% less variability' distorted the perceived impact of the clamp study outcomes and implied that less 'within-patient variability' would have definitive clinical benefit. The Panel considered

that this matter was inextricably linked to its rulings of breaches of the Code immediately above. A breach of Clause 7.2 was ruled. The Panel noted that the alleged breach of Clause 7.8 related to the visual prominence of the claim '75% Less Variability'. The Panel noted that Clause 7.8 stated that all artwork including illustrations, graphs and tables must conform to the letter and spirit of the Code and, when taken from published studies, a reference must be given. Graphs and tables must be presented in such a way as to give a clear, fair, balanced view of the matters with which they dealt, and must not be included unless they were relevant to the claims or comparisons being made. The Panel noted its comments above and considered that in the context of the page in question, the prominence of the claim in question and the Y axis labelling of the bar chart did not give a fair and balanced view of matters nor did it enable the nature of the data presented to be readily understood. A breach of Clause 7.8 was ruled.

The Panel noted that beneath the claim '75% Less Variability' in green font followed, in smaller black font:

> 'Tresiba was associated with **four-times lower within-patient day-to-day variability** in total glucose-lowering effect compared with insulin glargine U100.'
>
> This was followed by '**Benefits of lower variability**:
>
> - A potentially lower risk of hypo- and hyperglycaemia
> - Potentially aids titration to glycaemic targets'.

The Panel noted its comments above about Heise *et al* and the study's limitations. The Panel also noted its comments above about the impression created by the page in question. The Panel considered that use of the word 'potentially' in each of the bullet points did not negate the primary unequivocal impression given by the page and triple page spread including the unqualified bold subheading to the bullet points 'Benefits of lower variability'. The Panel considered that within the context of the page in question the claim of benefits of lower variability would be seen as a claim for Tresiba as would the two bullet points. The two claims 'A potentially lower risk of hypo- and glycaemic attacks' and 'Potentially aids titration to glycaemic targets' were misleading. A breach of Clause 7.2 was ruled.

The Panel noted that the safety section of Heise *et al* stated that 'In total 100 confirmed hypoglycaemic episodes were observed with [Tresiba] compared with 95 episodes with [insulin glargine]' and 'fewer confirmed nocturnal hypoglycaemic episodes were reported for [Tresiba] (16 episodes in 9 subjects) than iGlar (26 episodes in 13 subjects)' and that 'The observed number of hypoglycaemic episodes might be artificially high due to the fixed dosing level of 0.4U/kg of [Tresiba] and [insulin glargine]'. The Panel noted its comments above about the misleading impression given by the page including the two bullet points in question. The Panel did not consider that the primary impression given by the bullet points in question could be substantiated by Heise *et al* as alleged and a breach of Clause 7.4 was ruled.

2 Claim '142 Fewer Nocturnal Hypoglycaemic Events'

This claim appeared on page 4 of the leavepiece which was headed 'Tresiba achieves similar reductions in HbA_{1c} versus insulin glargine U100 but with a significantly lower risk of nocturnal hypoglycaemia'. It was followed by a graph titled 'Nocturnal confirmed hypoglycaemia in patients on basal-bolus, with type 1 diabetes over 105 weeks'. Both were referenced to Bode *et al*. The graph included a box stating '25% lower risk (p=0.02)'. To the right of the graph

appeared the claim in question '142 Fewer Nocturnal Hypoglycaemic Events' in large green font followed, in smaller black font, by 'for every 100 patients treated with Tresiba per year versus insulin glargine U100' which was referenced to Bode *et al*, Data on file and Ratner *et al* (2013). Directly beneath, in the same size font were the absolute rates per patient-year of exposure (Tresiba 3.9 episodes vs 5.3 episodes for glargine U100) followed by the statement 'There was no significant difference in the rate of confirmed overall hypoglycaemic episodes for Tresiba versus insulin glargine U100 in patients with type 1 diabetes *(p=ns)*'.

COMPLAINT

Sanofi alleged that the claim **'**142 Fewer Nocturnal Hypoglycaemic Events' was misleading and exaggerated the effect of Tresiba vs glargine U100. The very large font size and undue emphasis of the large sized number in contrast to the much smaller font size used below 'for every 100 patients ...' was misleading as it was not clear at first sight that this number was relevant specifically to 100 patients. The illustration using disproportionate font sizes, exaggerated the reported hypoglycaemic event difference between the two insulins. This was especially pertinent as there was no significant difference in the rate of confirmed overall hypoglycaemic episodes for Tresiba vs insulin glargine U100 in patients with type 1 diabetes as detailed in the small font sized statement at the bottom right-hand side of the page at issue. Sanofi alleged a breach of Clause 7.2.

RESPONSE

Novo Nordisk noted that page 4 of the leavepiece presented hypoglycaemia data from a randomised controlled clinical trial (Bode *et al*, Heller *et al* 2012 and Ratner *et al*). The company stated that the font size used for the claim '142 Fewer Nocturnal Hypoglycaemic Events' was reasonable and not disproportionate to the size of the graph which illustrated this difference. The statement '... for every 100 patients' was sufficiently prominent to be clear to the reader despite a difference in font size since the 'per 100 patients' was directly beneath and had also been enlarged and in black font to make it prominent to the reader. In addition, the statement '142 Fewer Nocturnal Hypoglycaemic Events …' did not make sense in isolation without a denominator, therefore readers would naturally be drawn to read on to make scientific sense of the information in front of them. Directly below, in the same size font were the absolute rates which again were clear for the reader to interpret for additional information. This gave a fully balanced set of statistics for the reader to interpret the results.

Novo Nordisk submitted that the statement regarding no significant difference in the rate of confirmed hypoglycaemic episodes was also sufficiently prominent and in a black font and therefore was not misleading. The company denied a breach of Clause 7.2.

Novo Nordisk submitted that the leavepiece was accurate, not misleading and was sufficiently complete to enable readers to form their own opinion of the therapeutic value of Tresiba.

PANEL RULING

The Panel noted that the graph showed a 25% lower risk of nocturnal hypoglycaemia with Tresiba compared with insulin glargine U100; a prominent downward arrow bore the claim ' 25% lower risk', p=0.02. The graph, and the claim in question '142 Fewer Nocturnal Hypoglycaemic Events' were each referenced to Bode *et al* which concluded that patients with type 1 diabetes who continued Tresiba therapy experienced similar long-term fasting plasma

glucose and HbA_{1c} to that of patients treated with insulin glargine but with a lower risk of nocturnal hypoglycaemia. The study authors noted that the similarity in overall confirmed hypoglycaemic episodes between groups suggested that the hypoglycaemic benefit of Tresiba was not observed during the day. The study showed that rates of nocturnal hypoglycaemia were 25% lower with Tresiba than insulin glargine U100.

The bold and prominent claim in question '142 Fewer Nocturnal Hypoglycaemic Events' appeared adjacent to the graph and in the same green font as the prominent page heading. The qualification 'for every 100 patients treated with Tresiba per year versus insulin glargine U100' appeared in much smaller black font, as a distinct and separate paragraph below and did not immediately appear to be part of the claim in question. This was compounded by the fact that the font colour and prominence of the claim in question and the page heading visually linked the two drawing the reader's eye away from the qualification to the claim in question. In the Panel's view it would not be immediately obvious that the separate paragraph beneath was in fact a continuation of the claim above and formed part of the same sentence.

The Panel noted that the statement that there was 'no significant difference in the rate of confirmed overall hypoglycaemic episodes for Tresiba versus insulin glargine U100 in patients with type 1 diabetes (p=ns)' was the third paragraph below the claim in question again in black smaller font.

The Panel considered that the claim '142 Fewer Nocturnal Hypoglycaemic Events' exaggerated the reported hypoglycaemic event difference between the two insulins. The Panel disagreed with Novo Nordisk's submission that the statement regarding no significant difference in the rate of confirmed hypoglycaemic episodes was sufficiently prominent and considered that it did not negate the overall impression of the page. Nor in the Panel's view and for the reasons stated above was the claim in question suitably qualified by the paragraph immediately beneath. The Panel considered that the comparison was misleading in that regard and potentially exaggerated the effect of Tresiba and a breach of Clauses 7.2 was ruled.

Complaint received **20 February 2017**

Case completed **7 July 2017**