CASE AUTH/2152/8/08

NOVO NORDISK v SANOFI-AVENTIS

Promotion of Lantus

Novo Nordisk complained about a mailer and two leavepieces produced by Sanofi-Aventis that promoted Lantus (insulin glargine). Novo Nordisk marketed Levemir (insulin detemir).

The detailed response from Sanofi-Aventis is given below.

The claim '24-hour efficacy' appeared as a heading to a section in the mailer as did the claim 'Once daily'. The section headed 'Once daily' featured a table headed '12 month comparison of Lantus vs insulin detemir (n=582)' referenced to Rosenstock *et al* (2008). The table compared Lantus and Levemir with regard to reduction in HbA1c, percentage of patients treated once daily and the total daily insulin dose.

Whilst Novo Nordisk acknowledged that the claim 'Once daily' was substantiated by the Lantus summary of product characteristics (SPC), it had major concerns regarding the data in the table from a trial where Levemir and Lantus were compared as part of an initial basal-oral insulin regimen in insulin-naïve type 2 diabetics (Rosenstock *et al*). By the end of the trial 55% of patients randomized to Levemir used twice daily injections (45% remained on once daily injection) whilst all of the Lantus patients used the preparation once daily. The table highlighted the proportion of once daily Levemir users 45% by the end of the trial and quoted the proportion of twice daily users in brackets below (55% twice daily). All patients had taken Lantus once daily.

With regard to total daily insulin dose, it was stated in the table that the final Levemir dose for the combined (once and twice daily users) arm was 0.78U/kg*. The footnote gave the separate figures ie once daily 0.52U/kg, twice daily 1U/kg. The figure for Lantus was 0.44U/kg. Sanofi-Aventis had deliberately used the higher dose for the combined group to mislead readers that there was a massive dose difference between Lantus and Levemir when both were used once daily. The footnote provided important facts in order to fairly compare the doses and should have been placed in the table in the same manner as that for the percentage of patients using once or twice daily Levemir. Sanofi-Aventis had noted that all the data regarding doses could be found in the material. However, Novo Nordisk's major concern was about the way these data were presented.

Novo Nordisk alleged that the presentation of the information in the mailer strongly suggested Sanofi-Aventis' deliberate intention to disparage Levemir. Novo Nordisk alleged that the claims '24-hour efficacy' and 'Once daily' implied that Levemir predominantly needed to be taken twice daily which was misleading and disparaging; Sanofi-Aventis had disregarded other data which supported the once daily use of Levemir. The only direct comparison of these two insulin preparations, a clamp investigation in type 2 diabetes (Klein *et al* 2007), showed no difference in terms of duration of action. This indicated a similar use of these preparations in a clinical setting in terms of the number of daily injections. This was further confirmed in an analysis of all of the available Lantus or Levemir clamp trials (Heise *et al* 2007). The authors concluded that both preparations were suitable for once daily routine use in type 2 diabetes and could often be used once daily in type 1 diabetics. Furthermore clinical trials also suggested that Levemir could be used once daily in type 2 diabetes. In a randomized clinical trial, Philis-Tsimikas *et al* (2006), patients using exclusively once daily Levemir in combination with oral antidiabetic medicines achieved a significant improvement of 1.5% in HbA1c, a similar reduction to that observed in Rosenstock *et al*.

Novo Nordisk alleged that the claims '24 hour efficacy' and 'Once daily' implied that Sanofi-Aventis could provide substantiation from experimental and clinical studies. The substantiation was also misleading since the experimental data came from type 1 diabetes, whilst the clinical data came from type 2 diabetes. Sanofi-Aventis had not considered the only clamp trial which directly compared the two products (Klein *et al*). This promotional material had a picture of people with type 2 diabetes phenotype on the front and provided results from a clinical trial comparing Lantus and Levemir in type 2 diabetes. Therefore the only possible reason why Sanofi-Aventis had chosen to show the results from a clamp trial conducted in type 1 diabetes, instead of using available type 2 data, was to 'cherry-pick' the only clamp trial with favourable results.

Novo Nordisk alleged that the careful selection of trials and studies with favourable results for Lantus compared with Levemir, whilst disregarding other evidence, was unfair and misleading and disparaged Levemir.

The Panel noted that the table at issue detailed Rosenstock *et al* which had compared Lantus and Levemir over 12 months in insulin-naïve type 2 diabetics. It was not a comparison of only once daily usage of the two insulin preparations. At the end of the study 100% of Lantus patients were on once daily injections whereas 45% of Levemir patients were so treated with 55% being on twice

daily injections. The mean daily insulin dose for the Lantus group (n=248) was 0.44U/kg whilst for the Levemir group (n=227) it was 0.78U/kg (0.52U/kg on once daily (n=102) and 1U/kg on the twice daily dosing (n=125)). The Panel considered that it was important for prescribers to know that when treating insulin-naïve type 2 diabetics, a significant proportion were likely to need Levemir twice daily and that overall insulin use might be increased with Levemir compared with Lantus. Nonetheless the Panel considered that the presentation of the data in the table was misleading; it was unclear that the figure of 0.78U/kg given for Levemir related to the whole of that patient group given that the row of data immediately above specifically referred to once daily injections. Readers had to refer to the asterisked footnote to be able to understand the data fully. The Panel considered that in that regard the table was misleading and a breach of the Code was ruled.

The Panel did not consider that the information in the table disparaged Levemir as alleged.

Novo Nordisk further complained about a leavepiece entitled 'Why choose Lantus to complement OADs [oral antidiabetics]?'. The two centrefold pages were at issue. The left-hand page was headed 'Lantus can help patients who are uncontrolled on OADs' followed by a patient profile and details of a study by Yki-Järvinen *et al* (2007). The page concluded 'Lantus + OADs can give patients up to a 2% reduction in HbA1c in 24 weeks (p<0.001 vs baseline)'.

The right-hand page was headed 'Simple self titration with Lantus' which included a recommendation from Monnier and Colette (2006) to titrate '… up to 0.5U/kg of basal insulin; after that consider adding a rapid-acting insulin to avoid weight gain'.

The leavepiece had been voluntarily withdrawn by Sanofi-Aventis following inter-company dialogue in relation to Case AUTH/2141/7/08.

Novo Nordisk noted that the leavepiece promoted the initiation of Lantus in patients with type 2 diabetes uncontrolled on oral antidiabetic medicines. The leavepiece included a table that contained a patient profile from the INITIATE study (Yki-Järvinen *et al*) and beneath the table the claim 'Lantus + OADs can give patients up to a 2% reduction in HbA1c in 24 weeks (p<0.001 vs baseline)'. The INITIATE study showed that the final Lantus dose for the two arms was 0.60 and 0.64U/kg. In contradiction with this finding the facing page suggested that Lantus be titrated up to a 0.5U/kg dose and after that the addition of rapid-acting insulin to avoid weight gain should be considered. Clearly the INITIATE study was chosen to create the patient profile because the improvement of Hb1Ac was the greatest from all the trials conducted on the basal-oral use of Lantus. Novo Nordisk alleged that using these two claims together in the same leavepiece misled health professionals to believe that by using a dose of 0.5U/kg a 2% reduction in Hb1Ac could be achieved. In fact, the 2% reduction achieved in the INITIATE study was at the larger dose as mentioned above.

The Director noted that the leavepiece had been withdrawn due to different allegations. It was not clear that Sanofi-Aventis would not use the claims now at issue again. Thus the Director considered that inter-company dialogue had not been completely successful and the matter was referred to the Panel.

The Panel noted the title of the leavepiece 'Why choose Lantus to complement OADs' was followed on the inside page by 'Lantus can help patients who are uncontrolled on OADs' beneath which information was given about initiating treatment of type 2 diabetes with Lantus. The next page was headed 'Simple self titration with Lantus'. The Panel considered that many readers would assume that the leavepiece set out a normal course of events following initiation of Lantus. The context of claims was an important consideration.

The Panel considered that, without any statement to the contrary, readers would assume that the data regarding a 2% reduction in HbA1c was linked to the statements regarding dose titration which was not so. The Panel did not consider that readers would see the pages as distinct and separate in their own right as submitted by Sanofi-Aventis. Although the dose of Lantus (62 units) used to achieve a 2% reduction in HbA1c was stated it was impossible for the reader to know how this compared to the maximum titrated dose (0.5U/kg) recommended by Monnier and Colette. From the published study (Yki-Järvinen *et al*) it appeared that the Lantus dose which resulted in a 2% reduction in HbA1c in U/kg was 0.66U/kg (given that the mean weight at baseline had been 93.8kg and the mean dose of insulin was 62 units). (Novo Nordisk had calculated a dose of 0.64U/kg). The Panel considered that viewed together the pages gave a misleading impression and a breach of the Code was ruled.

Novo Nordisk further complained about a page in a leavepiece headed '… but what about weight gain?' which set out data for weight gain in type 1 and type 2 diabetes. The section about type 2 diabetes included a bar chart comparing of the mean weight change after 1 year with Lantus once daily (3.9kg) and twice daily Levemir (3.7kg) (p=NS). The bar chart was referenced, *inter alia*, to Rosenstock *et al*.

The leavepiece had been voluntarily withdrawn by Sanofi-Aventis following inter-company dialogue in relation to Case AUTH/2141/7/08.

Novo Nordisk was concerned about a claim about the weight gain in type 2 diabetes. Although the weight gain was significantly lower after insulin initiation with Levemir in Rosenstock *et al*, Sanofi-

Aventis had deliberately implied that there was no difference in this regard between the two products. The prominent bar chart was proof of this intention. Novo Nordisk noted that the Levemir SPC stated 'Studies in patients with type 2 diabetes treated with basal insulin in combination with oral antidiabetic drugs demonstrated that glycaemic control (HbA1c) with Levemir is comparable with NPH insulin and insulin glargine and associated with less weight gain …'.

Sanofi-Aventis had repeatedly tried to suggest that Lantus resulted in the same weight gain, after insulin initiation as part of a basal-oral regimen, as Levemir and referred to a previous case (Case AUTH/2038/8/07) in that regard.

Therefore Novo Nordisk alleged that the presentation of the weight gain data in type 2 diabetes, which tried to imply the same message as had been ruled in breach earlier, was misleading. Furthermore Sanofi-Aventis highlighted itself that it compared weight results with once-daily Lantus and twice-daily Levemir. Although twice-daily use was permitted by the Levemir SPC, it was not the usual and recommended way in insulin initiation. The Levemir SPC suggested starting with once daily in combination with OADs in type 2 diabetics. The only reason to use the twice daily subgroup from Rosenstock *et al* (instead of the more relevant once daily users or the combined cohort of the once daily and twice daily users) was to find the only piece of information in the medical literature which could substantiate the weight comparison claim at issue.

The Panel noted that the page headed '… but what about weight gain?' was divided into two sections – one related to type 1 diabetes whilst the other referred to type 2 diabetes. The type 2 diabetes section featured a visually prominent bar chart showing the weight change after one year with once daily Lantus (+3.9kg) and twice daily Levemir (+3.7kg) (p=NS). Although it was also stated that weight gain over one year with Lantus plus OADs was only 0.9kg more than that seen with Levemir plus OADs (p=0.01) thus acknowledging a greater weight gain in the Lantus group, this written claim was much less obvious to the reader than the bar chart.

The bar chart detailed the results from Rosenstock *et al* in which insulin-naïve type 2 diabetes had been treated with Lantus or Levemir. Although all Lantus patients had remained on once daily injections, 55% of Levemir patients had progressed to twice daily injections. The weight gain seen with the two Levemir dosing regimens varied and in the Panel's view it was important that prescribers knew all of the facts. The bar chart had detailed once daily Lantus vs twice daily Levemir where the difference in weight gain between the two was in favour of Levemir and stated as being non-significant (the statistical significance was not stated in Rosenstock *et al* but appeared to have been taken from a Novo Nordisk review of Levemir therapy and effect on body weight). The results for once daily Lantus vs once daily Levemir, as reported by Rosenstock *et al* and applicable to 45% of patients, were not stated in the leavepiece. This would have shown a statistically significant advantage for Levemir (+2.3kg vs +3.9kg, p<0.001). The Panel considered that by reporting only some of the Rosenstock *et al* data the leavepiece was incomplete and misleading in that regard. Prescribers had not been given all of the information upon which to make a fully informed prescribing choice. A breach of the Code was ruled.

The Panel did not consider that the weight gain data in type 2 diabetes was not capable of substantiation as alleged and no breach of the Code was ruled.

The Panel did not consider that Sanofi-Aventis had failed to maintain high standards. No breach of the Code was ruled including no breach of Clause 2.

Novo Nordisk Limited complained about a mailer (LAN08/1041) and two leavepieces (LAN08/1038 and LAN08/1039) produced by Sanofi-Aventis that promoted Lantus (insulin glargine). Novo Nordisk marketed Levemir (insulin detemir).

Novo Nordisk stated that inter-company dialogue had failed to resolve matters.

This case was considered under the 2008 Constitution and Procedure. The clauses cited, 2, 7.2, 7.4, 8.1 and 9.1, were the same in the 2006 Code as in the 2008 Code. Thus the Panel used the 2008 Code.

1 Mailer – 'Why choose Lantus?' (ref LAN08/1041)

This was used once in early 2008.

The claim '24-hour efficacy' appeared as a heading to a section as did the claim 'Once daily'. The section headed 'Once daily' featured a table headed '12 month comparison of Lantus vs insulin detemir (n=582)' referenced to Rosenstock *et al* (2008). The table compared Lantus and Levemir with regard to reduction in HbA1c, percentage of patients treated once daily and the total daily insulin dose.

COMPLAINT

Novo Nordisk noted that there was an ongoing case (Case AUTH/2141/7/08) regarding the '24-hour efficacy' claim, thus it did not address this issue. However its complaint about the claim 'Once daily' (see below) would partially deal with the '24-hour efficacy' claim in order to put it into a different context and show how Sanofi-Aventis manipulated the data from different trial settings in order to imply that Lantus had trial results to substantiate the '24-hour efficacy' and 'Once daily' claims from experimental and clinical perspectives.

Whilst Novo Nordisk acknowledged that the claim

'Once daily' was substantiated by the Lantus summary of product characteristics (SPC), it had major concerns regarding the data in the table which came from a randomized clinical trial where Levemir and Lantus were compared as part of an initial basal-oral insulin regimen in insulin-naïve type 2 diabetics (Rosenstock *et al*). By the end of the trial 55% of patients randomized to Levemir used twice daily injections (45% remained on once daily injection) whilst all of the Lantus patients used the preparation once daily.

With regard to the percentage of patients treated with a once daily injection, the table highlighted the proportion of once daily Levemir users (45%) by the end of the trial and quoted the proportion of twice daily users in brackets below (55%). All patients had taken Lantus once daily.

With regard to total daily insulin dose, it was stated in the table that the final Levemir dose for the combined (once and twice daily users) arm was 0.78U/kg*. The footnote gave the separate figures ie once daily 0.52U/kg, twice daily 1U/kg. The figure for Lantus was 0.44U/kg. Sanofi-Aventis had deliberately used the higher dose for the combined group to mislead readers that there was a massive dose difference between Lantus and Levemir when both were used once daily. The additional information in the footnote provided important facts in order to fairly compare the doses and should have been placed in the table in the same manner as that for the percentage of patients using once or twice daily Levemir. Sanofi-Aventis had noted that all the data regarding doses could be found in the material. However, Novo Nordisk's major concern was not related to using only selective results from a dose perspective but the way these data were presented in the mailer. Sanofi-Aventis' argument about the use of clamp study data was completely irrelevant from a dose perspective.

Novo Nordisk alleged that the presentation of the information in the mailer strongly suggested Sanofi-Aventis' deliberate intention to disparage Levemir. Novo Nordisk alleged that the claims '24-hour efficacy' and 'Once daily' implied that Levemir predominantly needed to be taken twice daily which was misleading and disparaging; Sanofi-Aventis had disregarded other data which supported the once daily use of Levemir. In the only head-to-head comparison of these two insulin preparations, a clamp investigation in type 2 diabetes (Klein *et al* 2007), there was no difference in terms of duration of action. This indicated a similar use of these preparations in a clinical setting in terms of the number of daily injections. This was further confirmed in an analysis of the results from all the available clamp trials investigating either Lantus or Levemir (Heise *et al* 2007). The authors concluded that both preparations were suitable for once daily routine use in type 2 diabetes and could often be used once daily in type 1 diabetics. Furthermore clinical trials also suggested that Levemir could be used once daily in type 2 diabetes. In a randomized clinical trial, Philis-Tsimikas *et al* (2006), patients using exclusively once daily Levemir in combination with oral antidiabetic medicines achieved a significant improvement of 1.5% in HbA1c, a similar reduction to that observed in Rosenstock *et al*.

Novo Nordisk alleged that the claims '24 hour efficacy' and 'Once daily' implied that Sanofi-Aventis could provide substantiation from both experimental (clamp) trials and clinical studies (randomized clinical trials). In fact the substantiation used was also misleading since the experimental data came from type 1 diabetes, whilst the clinical data came from type 2 diabetes. Sanofi-Aventis had not considered the only clamp trial which compared the two products head-to-head (Klein *et al*). This promotional material had a picture of people with type 2 diabetes phenotype on the front and provided results from a clinical trial comparing Lantus and Levemir in type 2 diabetes. Therefore the only possible reason why Sanofi-Aventis had chosen to show the results from a clamp trial conducted in type 1 diabetes, instead of using available type 2 data, was to 'cherry-pick' the only clamp trial with favourable results.

Novo Nordisk alleged that the selection of trials and studies with favourable results for Lantus compared with Levemir, whilst disregarding other available evidence, was an unfair and misleading and disparaged Levemir in breach of Clauses 7.2, 8.1 and 9.1 of the Code.

RESPONSE

Sanofi-Aventis noted that Novo Nordisk was concerned about the following table which appeared beneath the claim 'Once daily':

12-month comparison of Lantus vs insulin detemir (n=582)

	Lantus (insulin glargine)	Insulin detemir
Reduction in HbA1c	**1.5% reduction**	1.4% reduction (p=NS between treatments)
Once-daily injection (% of patients)	**100%**	45% (55% twice-daily)
Total daily insulin dose	**0.44U/kg**	0.78 U/kg*

Therapies were add-ins to oral treatments in patients with type 2 diabetes.
*Once-daily 0.52U/kg; twice-daily 1U/kg.

Sanofi-Aventis noted that Novo Nordisk was concerned that the total daily insulin dose for Levemir (in comparison with Lantus) was for the combined group of Levemir patients (both once daily and twice daily dosing together). Novo Nordisk alleged that this disparaged Levemir through 'using the higher dose for the combined group' to 'highlight that there was a massive dose

difference between Lantus and Levemir when used once daily', and that the additional information presented in the footnote should have been included in the table. Sanofi-Aventis disagreed.

Firstly, presenting the combined mean daily dose was the only scientific way to compare the two products. The study was designed to compare patients using Lantus (n=291) with all patients using Levemir (n=291), irrespective of frequency of dosing. The primary endpoints were described in terms of the total patient cohort for Levemir (once daily and twice daily dosing combined); Sanofi-Aventis had therefore made the most appropriate comparison by including the combined Levemir cohort data as the primary data cohort within the table.

Secondly, contrary to the allegation above, the dose in the combined Levemir group (0.78U/kg) was not the largest dose observed in the study, 1U/kg for patients receiving Levemir twice daily. Had Sanofi-Aventis included that figure in the table then that would have inappropriately drawn attention to 'a massive dose difference between Lantus and Levemir'. As this was not reflected in the item, Sanofi-Aventis disagreed with the allegation that the table was misleading and disparaged Levemir.

In summary, with the exception of the error already admitted and dealt with by inter-company dialogue, Sanofi-Aventis submitted that it did not consider that the table misled nor disparaged, and through these considerations and the manner in which the identified error had been dealt with high standards had been maintained.

Sanofi-Aventis noted that following these allegations, Novo Nordisk asserted that Sanofi-Aventis had aimed to disparage Levemir, stating that the use of 'Once daily' and '24-hour efficacy' in relation to Lantus suggested that this was not the case for Levemir. Sanofi-Aventis did not consider that any disparagement had occurred, either directly or implied. The two claims were only about Lantus, had been demonstrated in peer reviewed, published clinical trials and were substantiable as such and consistent with the SPC. Further information about Levemir was similarly derived from peer reviewed, published clinical trials, and was entirely consistent with its marketing authorization.

The SPC recommended that Levemir, in combination with oral antidiabetic agents, be initiated once daily. This implied that although once daily dosing was appropriate when starting insulin, as the dose was increased to achieve control of the condition twice daily therapy might be necessary. This was in keeping with Rosenstock *et al*, which had been incorporated into Levemir's SPC – although once daily initiation occurred in all patients, 55% subsequently required an increase to twice daily dosing to achieve adequate glycaemic control. The SPC similarly stated that as part of a basal-bolus regimen Levemir 'should be administered once or twice daily depending on patients' needs'.

Sanofi-Aventis noted that Novo Nordisk then suggested that in using 'Once daily' and '24-hour efficacy' claims Sanofi-Aventis implied that these could be substantiated from clamp studies and randomised clinical studies. It was not clear how such an implication was made. Regardless, Sanofi-Aventis disagreed with this suggestion as isoglycaemic clamp studies were widely considered the best and most appropriate way to assess duration of action of insulin, measuring specifically the period of time over which insulin exerted a pharmacological action; they were therefore the most appropriate data source to substantiate a claim of '24-hour efficacy'. This opinion was clearly made in Heise *et al* cited by Novo Nordisk and was an argument that had even been successfully proposed by Novo Nordisk in Case AUTH/1622/8/04.

In addition to the clamp studies, a number of randomised clinical trials supported the claim of once daily Lantus dosing in type 2 diabetics. Sanofi-Aventis provided a summary of these studies which showed that, following effective titration, excellent glycaemic control (ie HbA1c values of approximately 7%), was achieved using Lantus once daily. The clinical evidence therefore also supported the 'Once daily' claim.

Finally, with respect to the observation that the selection of clamp studies related to patients with type 1 diabetes but not type 2 diabetes, Sanofi-Aventis submitted that this was the approach adopted in the academic community as type 1 diabetes was best suited to demonstrate the action of an insulin in the absence of any confounding factors (such as endogenous insulin or insulin resistance, both of which might be present in patients with type 2 diabetes). Again, Novo Nordisk had previously successfully argued that clamp studies in patients with type 1 diabetes were appropriate to support such claims on the basis that it was important to examine 'the properties of insulin and not the type of diabetes' (Case AUTH/1622/8/04).

That said evidence from two published clamp studies in patients with type 2 diabetes Lantus maintained a 24-hour duration of action. In both studies, and at all doses, a single injection of Lantus was effective at preventing hyperglycaemia throughout the 24-hour duration of each study.

In summary, Sanofi-Aventis submitted that the claims '24-hour efficacy' and 'Once daily' were substantiated by the available scientific literature, reflecting an up-to-date evaluation of all applicable evidence, were consistent with the SPC, and that no breach of the Code had occurred.

PANEL RULING

The Panel noted that the table at issue detailed the results from Rosenstock *et al* which had compared Lantus and Levemir over 12 months in insulin-naïve type 2 diabetics. It was not a comparison of only

once daily usage of the two insulin preparations. At the end of the study 100% of Lantus patients were on once daily injections whereas 45% of Levemir patients were so treated with 55% being on twice daily injections. The mean daily insulin dose for the Lantus group (n=248) was 0.44U/kg whilst for the Levemir group (n=227) it was 0.78U/kg (0.52U/kg on once daily (n=102) and 1U/kg on the twice daily dosing (n=125)). The Panel considered that it was important for prescribers to know that when treating their insulin-naïve type 2 diabetics, a significant proportion of them were likely to need Levemir twice daily and that overall insulin use might be increased with Levemir compared with Lantus. Nonetheless the Panel considered that the presentation of the data in the table was misleading; it was unclear that the figure of 0.78U/kg given for Levemir related to the whole of that patient group given that the row of data immediately above specifically referred to once daily injections. Readers had to refer to the asterisked footnote to be able to understand the data fully. The Panel considered that in that regard the table of data was misleading and a breach of Clause 7.2 was ruled.

The Panel did not consider that the information in the table disparaged Levemir as alleged. Thus no breach of Clause 8.1 was ruled. The Panel noted its rulings and did not consider that high standards had not been maintained. No breach of Clause 9.1 was ruled.

2 Leavepiece – 'Why choose Lantus to complement OADs [oral antidiabetics]?' (ref LAN08/1038)

This leavepiece had been voluntarily withdrawn by Sanofi-Aventis following inter-company dialogue in relation to Case AUTH/2141/7/08.

The two centrefold pages of the leavepiece were at issue. The left-hand page was headed 'Lantus can help patients who are uncontrolled on OADs' followed by a patient profile and details of a study by Yki-Järvinen *et al* (2007). The page concluded 'Lantus + OADs can give patients up to a 2% reduction in HbA1c in 24 weeks (p<0.001 vs baseline)'.

The right-hand page was headed 'Simple self titration with Lantus' which included a recommendation from Monnier and Colette (2006) to titrate '… up to 0.5U/kg of basal insulin; after that consider adding a rapid-acting insulin to avoid weight gain'.

COMPLAINT

Novo Nordisk noted that the leavepiece promoted the initiation of Lantus in patients with type 2 diabetes uncontrolled on oral antidiabetic medicines. The leavepiece included a table that contained a patient profile from the INITIATE study (Yki-Järvinen *et al*) and beneath the table the claim 'Lantus + OADs can give patients up to a 2% reduction in HbA1c in 24 weeks (p<0.001 vs baseline)'. The INITIATE study showed that the final Lantus dose for the two arms was 0.60 and 0.64U/kg. In contradiction with this finding on the facing page of the leavepiece it was suggested that Lantus be titrated up to a 0.5U/kg dose and after that the addition of rapid-acting insulin to avoid weight gain should be considered. Clearly the INITIATE study was chosen to create the patient profile because the improvement of Hb1Ac was the greatest from all the trials conducted on the basal-oral use of Lantus. Novo Nordisk alleged that using these two claims together in the same leavepiece misled health professionals to believe that by using a dose of 0.5U/kg a 2% reduction in Hb1Ac could be achieved. In fact, the 2% reduction achieved in the INITIATE study was at the larger dose as mentioned above. Novo Nordisk alleged a breach of Clause 7.2. In inter-company dialogue Sanofi-Aventis replied that the information it provided to health professionals from the two trials could be found on separate, stand-alone pages. The page related to INITIATE contained data about HbA1c improvement and the applied insulin dose in the trial, whilst the other page referred to the titration guide from the AT.LANTUS trial.

Novo Nordisk alleged that any promotional material should be considered as one piece; it should not provide data and suggestions which contradicted each other.

Although the page about the INITIATE trial provided information about the final insulin dose which was related with the relevant HbA1c improvement in the study, but it showed the final total dose [sic].

Novo Nordisk alleged that in this way readers did not have the information about the final U/kg dose, although this information could be found in the full publication. Since the U/kg dose from the INITIATE trial was in contradiction with the suggestion on the opposite page (adding rapid-acting insulin when the dose of basal insulin exceeded 0.5U/kg) Novo Nordisk alleged that readers might be misled into assuming that with the suggested maximum basal dose (ie 0.5U/kg) HbA1c could be improved by 2% (as it was seen in the INITIATE trial with the final dose of 0.64U/kg).

RESPONSE

Sanofi-Aventis stated that the leavepiece was designed to tell clinicians about the benefits of Lantus in patients with type 2 diabetes inadequately controlled on oral hypoglycaemic agents, and how patients could be advised to adjust their own dose so as to improve their diabetes control. The leavepiece had been withdrawn as a result of inter-company discussions with respect to Case AUTH/2141/7/08.

Sanofi-Aventis submitted that the leavepiece provided important information on the optimal use of Lantus in a responsible and appropriate manner.

The two pages, although facing, were distinct and separate in their own right and were separate in both nature and content. The left-hand page had a clear and discreet title 'Lantus can help patients who are uncontrolled on OADs'. The page described the results of a clinical trial (Yki-Järvinen *et al*) in terms of the improvement in glycaemic control achieved by adding Lantus to existing oral antidiabetic agents. The page provided information of the results of this study, and the dose used to achieve these results was clearly stated (in units). The right-hand page, also discreet, covered an entirely separate and discreet topic of 'Simple self titration with Lantus'. This described a suitable regimen from another study of Lantus in type 2 diabetes (Davies *et al* 2005). Here the measure of success quoted was the final dose achieved by the patient, not the level of glycaemic control achieved. Again, this final dose was clearly stated. In addition, a second recommendation was provided for clinicians to provide advice on an upper limit for Lantus titration above which they could consider adding a meal-time insulin for additional glycaemic control. Both pages made a very clear reference to the doses utilised in each study – 62 units on the left-hand page, 45 units on the right-hand page, and were provided in this format so as to enable the reader to compare the two pieces of evidence. The intended audience would readily identify that the two doses were different and that results on the left-facing page would not be replicated by following the advice on the right-facing page.

Sanofi-Aventis therefore submitted that the leavepiece provided important information to help inform clinicians and optimise the treatment of their patients and, rather than seeking to mislead, it met high standards and no breach of the Code had occurred.

PANEL RULING

The Director noted that the leavepiece had been withdrawn due to different allegations. It was not clear that Sanofi-Aventis would not use the claims now at issue again. Thus the Director considered that inter-company dialogue had not been completely successful and the matter was referred to the Panel for it to consider.

The Panel noted the title of the leavepiece 'Why choose Lantus to complement OADs' was followed on the inside page by 'Lantus can help patients who are uncontrolled on OADs' beneath which information was given about initiating treatment of type 2 diabetes with Lantus. The next page was headed 'Simple self titration with Lantus'. The Panel considered that many readers would assume that the leavepiece set out a normal course of events following initiation of Lantus. The context of claims was an important consideration.

The Panel considered that, without any statement to the contrary, readers would assume that the data regarding a 2% reduction in HbA1c was linked to the statements regarding dose titration which was not so. The Panel did not consider that readers would see the pages as distinct and separate in their own right as submitted by Sanofi-Aventis. Although the dose of Lantus (62 units) used to achieve a 2% reduction in HbA1c was stated it was impossible for the reader to know how this compared to the maximum titrated dose (0.5U/kg) recommended by Monnier and Colette. From the published study (Yki-Järvinen *et al*) it appeared that the Lantus dose which resulted in a 2% reduction in HbA1c in U/kg was 0.66U/kg (given that the mean weight at baseline had been 93.8kg and the mean dose of insulin was 62 units). (Novo Nordisk had calculated a dose of 0.64U/kg). The Panel considered that viewed together the pages gave a misleading impression and a breach of Clause 7.2 was ruled.

3 Leavepiece – 'Lantus – getting the balance right for your diabetes patients' (ref LAN08/1039)

This leavepiece had been voluntarily withdrawn by Sanofi-Aventis following inter-company dialogue in relation to Case AUTH/2141/7/08.

The complaint concerned a page headed '… but what about weight gain?' which set out data for weight gain in type 1 and type 2 diabetes. The section about type 2 diabetes included a bar chart comparing of the mean weight change after 1 year with Lantus once daily (3.9kg) and twice daily Levemir (3.7kg) (p=NS). The bar chart was referenced, *inter alia*, to Rosenstock *et al*.

COMPLAINT

Novo Nordisk was concerned about a claim about the weight gain in type 2 diabetes. Although the weight gain was significantly lower after insulin initiation with Levemir in Rosenstock *et al*, Sanofi-Aventis had deliberately implied that there was no difference in this regard between the two products. The prominent bar chart was proof of this intention. Novo Nordisk noted that the Levemir SPC stated 'Studies in patients with type 2 diabetes treated with basal insulin in combination with oral antidiabetic drugs demonstrated that glycaemic control (HbA1c) with Levemir is comparable with NPH insulin and insulin glargine and associated with less weight gain …'. A table of data in the SPC showed, *inter alia*, that at 52 weeks weight gain with Lantus was 4kg, with Levemir twice daily it was 3.7kg and with Levemir once daily it was 2.3kg.

Sanofi-Aventis had repeatedly tried to suggest to health professionals that Lantus resulted in the same weight gain, after insulin initiation as part of a basal-oral regimen, as Levemir. Novo Nordisk highlighted the previous ruling by the Appeal Board (Case AUTH/2038/8/07) that 'The Appeal Board considered that the claims at issue* [asterisk added by Novo Nordisk] were misleading as they did not reflect the totality of the data regarding the weight gain typically seen with Lantus and Levemir. The

Appeal Board upheld the Panel's ruling of a breach of Clause 7.2'.

Therefore Novo Nordisk alleged that the presentation of the weight gain data in type 2 diabetes, which tried to imply the same message as had been ruled in breach of Clause 7.2 earlier, misled health professionals and was in breach of Clause 2, 7.2 , 7.4 and 9.1. Furthermore Sanofi-Aventis highlighted itself that it compared weight results with once daily Lantus and twice daily Levemir. Although twice daily use was permitted by the Levemir SPC, it was not the usual and recommended way in insulin initiation. The Levemir SPC suggested starting with once daily in combination with OADs in type 2 diabetics. The only reason to use the twice daily subgroup from Rosenstock *et al* (instead of the more relevant once daily users or the combined cohort of the once daily and twice daily users) was to find the only piece of information in the medical literature which could substantiate the weight comparison claim at issue.

RESPONSE

Sanofi-Aventis noted that there were two comparisons made in the item with respect to type 2 diabetes and weight change:

Sanofi-Aventis submitted that the claim 'Weight gain over one year with Lantus + OADs was only 0.9kg more than the weight gain seen with Levemir + OADs (p=0.01)' was a direct comparison of the difference in weight gain in all patients using Levemir compared with all patients using Lantus in Rosenstock *et al*. The leavepiece clearly stated that weight gain was significantly greater in the Lantus group than the Levemir group, and provided both the difference (0.9kg) and level of significance (p=0.01), which was consistent with the published data. Therefore this information was accurate and substantiable, and met all the requirements of the Code.

Sanofi-Aventis noted that the claim 'In the 55% of patients taking Levemir twice daily there was no significant difference in weight gain compared with patients taking Lantus (3.7kg vs 3.9kg, p=NS)' was a direct comparison, from Rosenstock *et al*, of the weight gain seen in patients using Levemir twice daily, (which was the majority of patients, 55%), with patients using Lantus. The item clearly stated the levels of weight gain recorded in the study (3.7kg vs 3.9kg respectively), and the fact that there was no significant difference between these two groups. Sanofi-Aventis understood that it was this statement that was the origin of the complaint, through the fact that no significant difference in weight gain was reported in this statement.

Sanofi-Aventis noted that the Levemir SPC referred to the same study (although the figures were slightly different in the SPC than in the published report), and which stated that there was less weight gain for patients using Levemir twice daily (3.7kg) compared with Lantus (4kg). Although the SPC stated that there was less weight gain demonstrated in patients taking Levemir than other insulins, there were no significance levels provided in either the text or table to confirm whether the differences observed were significant.

Sanofi-Aventis noted that despite the absence of such confirmation in the SPC, it could substantiate the claim of no significant difference in weight gain between these two patient groups. Although the published paper, like the SPC, failed to provide the level of significance for this comparison, the quoted reference, a Novo Nordisk Drug Information Document, clearly indicated that the difference in weight gain was non-significant (stated as -0.55lbs, 95% CI -2.44, +1.36lbs, equivalent to -0.25kg, 95% CI -1.1, +0.62kg). In view of this, Sanofi-Aventis considered that this information was accurate and substantiable and met all the requirements of the Code.

Finally Sanofi-Aventis noted that Novo Nordisk referred to the previous case where weight gain was considered (AUTH2038/8/07), and to the Appeal Board's ruling at that time that a (different) claim made by Sanofi-Aventis of no significant difference in weight gain between patients using Lantus and Levemir did not reflect the totality of the evidence available. Novo Nordisk alleged that the leavepiece now at issue was contrary to findings of this case.

Sanofi-Aventis submitted that when this case was considered Novo Nordisk did not disclose its own drug information document confirming no significant difference in weight gain between these two groups of patients. In light of the information now known to exist, Sanofi-Aventis considered that the claim at issue was accurate, substantiable, met the requirements of the Code and was not in breach of the ruling in Case AUTH2038/8/07. The question remained as to whether the outcome in that case might have been different had Novo Nordisk disclosed this information (which was clearly relevant to the case) and had Sanofi-Aventis been able to refer to these facts and place them before the Panel and the Appeal Board when this was considered.

In conclusion, contrary to the allegation that this item was in breach of the Code and in breach of a previous ruling, Sanofi-Aventis submitted that the claims at issue could be substantiated and that high standards had been maintained throughout.

PANEL RULING

The Panel noted that the page headed '… but what about weight gain?' was divided into two sections – one related to type 1 diabetes whilst the other referred to type 2 diabetes. The type 2 diabetes section featured a visually prominent bar chart showing the weight change after one year with once daily Lantus (+3.9kg) and twice daily Levemir (+3.7kg) (p=NS). Although it was also stated that

weight gain over one year with Lantus plus OADs was only 0.9kg more than that seen with Levemir plus OADs (p=0.01) thus acknowledging a greater weight gain in the Lantus group, this written claim was much less obvious to the reader than the bar chart.

The bar chart detailed the results from Rosenstock *et al* in which insulin-naïve type 2 diabetes had been treated with Lantus or Levemir. Although all Lantus patients had remained on once daily injections, 55% of Levemir patients had progressed to twice daily injections. The weight gain seen with the two Levemir dosing regimens varied and in the Panel's view it was important that prescribers knew all of the facts so that they could advise their patients accordingly. The bar chart had detailed once daily Lantus vs twice daily Levemir where the difference in weight gain between the two was in favour of Levemir and stated as being non-significant (the statistical significance was not stated in Rosenstock *et al* but appeared to have been taken from a Novo Nordisk review of Levemir therapy and effect on body weight). The results for once daily Lantus vs once daily Levemir, as reported by Rosenstock *et al* and applicable to 45% of patients, were not stated in the leavepiece. This would have shown a statistically significant advantage for Levemir (+2.3kg vs +3.9kg, p<0.001).

The Panel considered that by reporting only some of the Rosenstock *et al* data the leavepiece was incomplete and misleading in that regard. Prescribers had not been given all of the information upon which to make a fully informed prescribing choice. A breach of Clause 7.2 was ruled.

The Panel did not consider that the weight gain data in type 2 diabetes was not capable of substantiation as alleged thus no breach of Clause 7.4 was ruled.

The Panel did not consider that Sanofi-Aventis had failed to maintain high standards and no breach of Clause 9.1 was ruled. Clause 2 was used as a sign of particular censure and reserved for such use. In the Panel's view the circumstances did not warrant a ruling of that clause.

Complaint received **5 August 2008**

Case completed **5 November 2008**