CASE AUTH/2045/9/07

LILLY v NOVO NORDISK

Promotion of Levemir

Lilly complained about an advertisement for Levemir (insulin detemir) issued by Novo Nordisk which was presented as an advertorial, entitled 'Levemir in type 2 diabetes an overview for primary care'. Under the subtitle 'Levemir-recent research and evidence' were the author's details. Prescribing information for Levemir was included. Lilly supplied a range of insulins.

The advertisement detailed four Novo Nordisk sponsored trials including PREDICTIVE (Lüddeke *et al*, 2006) which was a multinational, non-interventional, uncontrolled observational study designed to evaluate the incidence of serious adverse reactions, including major hypoglycaemic events, during Levemir treatment over 12, 26 or 52 weeks in type 1 or type 2 diabetics. The study involved 30,000 adults and children. The data included in the advertisement was a subanalysis of a defined cohort of European patients with type 2 diabetes, who were insulin naïve, initiated on Levemir and followed for 12 weeks (n=1,798).

The advertisement made a number of claims derived from the PREDICTIVE study. Lilly alleged that in the absence of an active comparator the claims that '… the initiation of Levemir is effective for patients with type 2 diabetes, without increasing the risk of hypoglycaemia' and 'the number of major hypoglycaemic events were significantly reduced for both daytime (p=0.021) and all (p=0.013)' could not be substantiated and were misleading. The second claim potentially compromised patient safety. The Levemir summary of product characteristics (SPC) stated 'Hypoglycaemia is a common undesirable effect. It may occur if the insulin dose is too high in relation to the insulin requirement. From clinical investigations it is known that major hypoglycaemia, defined as requirement for third party intervention, occurs in approximately 6% of patients treated with Levemir. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death'.

Hypoglycaemia was a significant and potential life-threatening side effect of insulin therapy and despite being listed in the Levemir SPC as common, nowhere in the advertisement had the risk with Levemir been highlighted and incidence data were not included. Lilly alleged that the advertisement was inconsistent with the Levemir SPC.

Lilly alleged that the claim 'Weight advantages with Levemir' was also at variance with the Levemir SPC which stated that 'Studies in patients with type 2 diabetes treated with basal insulin in combination with oral antidiabetic drugs demonstrates that glycaemic control (HbA1c) with Levemir is comparable to NPH insulin and insulin glargine and associated with less weight gain'. However, weight gain ranging from 0.7kg to 3.7kg was associated with Levemir treatment, varying with dosing and duration of treatment.

This was an uncontrolled observational study, and any findings in patients who had initiated Levemir would be confounded by a number of other factors including changes in other diabetes medicines and any lifestyle interventions which might be instituted as part of clinical practice. It was not possible to extrapolate from this data that any reported weight advantages were attributable to Levemir. Therefore the claim 'weight advantages with Levemir' was not capable of substantiation.

The advertisement stated that 52% of patients lost weight. This had been further detailed as: 43%, 26.3% and 15.6% of patients lost 1, 2 or 3kg respectively followed by the statement: 'Of those reviewed over half lost an average of more than 2.5kg in weight in only 12 weeks'. Lilly alleged it was very difficult to reconcile these ambiguous figures.

Lilly alleged that the undue emphasis placed on weight change within the advertisement, as evidenced by the large graph, was misleading. Weight change was not the primary objective of the study and indeed could be self-reported by patients, contributing to substantial bias. Therefore any claims of weight change derived from this study were misleading.

Lilly alleged that the advertisement was disguised promotion. It resembled an editorial written independently by a respected peer. Sponsorship of this advertisement had not been declared. It potentially misled health professionals and in particular might compromise patient safety. In Lilly's view this brought discredit to, and reduced confidence in, the pharmaceutical industry.

The Panel noted that the advertisement, presented in the style of an advertorial, was clearly headed 'Advertisement Feature'. The Panel considered that the layout and presentation of the advertisement was such that readers would not be misled as to its promotional nature. Prescribing information was included. The Panel thus did not consider that the advertisement was disguised promotion and so no breach was ruled. As it was clearly an advertisement no declaration of sponsorship was required. Prescribing information was clearly provided and so readers would know that the advertisement had been produced by Novo Nordisk. No breach of the Code was ruled.

The advertisement included a section describing the PREDICTIVE study. The claim 'This suggests that the initiation of Levemir is effective for patients with type 2 diabetes, without increasing the risk of hypoglycaemia' was not a stand alone claim; it came at the end of a block of text which discussed the 12 week data from a subgroup of the PREDICTIVE study. Previous text described the subgroup population ie type 2 diabetics who, at baseline were insulin-naïve and uncontrolled on oral anti-diabetic medicine. Adding Levemir to the existing oral therapy did not increase the risk of hypoglycaemia compared to baseline. In that regard the Panel considered that, given the context in which the claim appeared, it was clear that the comparison was with baseline ie oral antidiabetic therapy alone, and so in that regard the claim could be substantiated. The absence of an active comparator in this context did not mean that the claim could not be substantiated as alleged. No breach of the Code was ruled.

Similarly the claim 'The number of major hypoglycaemic events were significantly reduced for both daytime (p= 0.021) and all (p=0.013)' was not a stand alone claim but part of the text describing the PREDICTIVE study subgroup data. Lilly had not cited a clause and thus the Panel made no ruling on this point.

The Panel considered that prescribers would be well aware that insulin therapy was associated with a risk of hypoglycaemia. The advertisement at issue reported a reduced number of major hypoglycaemic episodes in type 2 diabetics before and after the addition of Levemir to their existing oral therapy. The advertisement did not state or imply that there was no risk of hypoglycaemia with Levemir therapy. In that regard, and given the audience to whom it was directed, the Panel did not consider that the advertisement was inconsistent with the particulars listed in the Levemir SPC. No breach of the Code was ruled.

The claim 'Weight advantages with Levemir' was a stand alone claim as it appeared as the heading to a section discussing the results from the PREDICTIVE study subgroup data for type 2 diabetics. The associated text referred to a mean decrease in weight of 0.6kg from baseline to week 12 in type 2 diabetics. It was further explained that during the study 52% of patients lost weight, 16% maintained the same weight and 32% had an increase in weight. A prominent bar chart depicted the results and in that regard emphasised the weight loss observed in the PREDICTIVE type 2 diabetes subgroup.

The Panel noted that the Levemir SPC stated that in studies in type 2 diabetes, patients treated with Levemir plus oral antidiabetic medicines gained less weight than those treated with Lantus plus oral antidiabetic medicines.

The Panel considered that with regard to changes to be expected in body weight, the advertisement was inconsistent with the Levemir SPC. In the Panel's view the advertisement implied that, in general, patients lost weight when Levemir was initiated whereas the SPC stated that they gained weight, albeit less than with other insulins. The Panel considered that although the advertisement reported the findings of the PREDICTIVE study, such findings were inconsistent with the particulars listed in the SPC. A breach of the Code was ruled. The Panel further considered that, in general, the claim 'Weight advantages with Levemir' was thus misleading and could not be substantiated. Breaches of the Code were ruled.

The Panel considered that the detailed weight data, as presented, was difficult to interpret as alleged. The percentages of patients losing 1,2 or 3kg were cumulative not absolute although this was not explained, thus it appeared that 15.6% of patients lost 3kg of weight, 26.3% lost 2kg of weight and 43% lost 1kg of weight which was not so. In that regard the Panel considered that the advertisement was misleading and ambiguous. A breach of Clause 7.2 of the Code was ruled. The Panel noted that Novo Nordisk had acknowledged that this part of the advertisement could have been written more clearly.

Upon appeal by Novo Nordisk of the Panel's rulings regarding weight the Appeal Board upheld the Panel's rulings of breaches of the Code.

Overall the Panel did not consider that either generally or in relation to the hypoglycaemic data that the advertisement warranted a ruling of a breach of Clause 2 of the Code.

Eli Lilly and Company Limited complained about a double page advertisement (ref UK/LM/0607/0040) for Levemir (insulin detemir) issued by Novo Nordisk Limited which appeared in Pulse, August 2007. The advertisement, which was presented as an advertorial, was entitled 'Levemir in type 2 diabetes an overview for primary care'. Under the subtitle 'Levemir-recent research and evidence' were the author's details. Prescribing information for Levemir appeared on the second page. Lilly supplied a range of insulins.

COMPLAINT

Lilly noted that it had set out its concerns about the advertisement in a letter to Novo Nordisk. Copies of the correspondence were provided. Lilly stated that it was clear that the two companies did not agree.

Lilly noted that Novo Nordisk had only responded to the comments made in respect of the risk of hypoglycaemia and the weight benefit of Levemir and not to comments that this advertisement did not declare sponsorship by Novo Nordisk and/or might be viewed as disguised promotion. Lilly noted Novo Nordisk's response 'In this article we have clearly specified that the weight change of -0.6kg was the mean for the whole subgroup …'. This was an explicit statement that the material was Novo Nordisk's and not Pulse's nor the author's. Lilly reiterated its concerns in respect of Clauses 9.10 and 10.1 of the Code, given this admission, together with the fact that the advertisement contained Levemir prescribing information and a Novo Nordisk promotional code.

Lilly's letter to Novo Nordisk stated that while the article had been authored by a GP, it had clearly been approved for promotional use by Novo Nordisk as evidenced by the inclusion of the prescribing information, promotional identifying code number and date of preparation. Indeed it appeared under the title 'Advertisement Feature'. Lilly alleged this advertisement was in breach of the Code on a number of grounds.

This article detailed four Novo Nordisk sponsored trials; the PREDICTIVE observational study (Lüddeke *et al*, 2006), a study comparing once-daily Levemir with NPH insulin (Philis-Tsimikas *et al*, 2006) and studies comparing insulin devices focusing on Novo Nordisk Flexpen (Lawton and Berg, 2001) and Innolet (Shelmet *et al*, 2003).

Lilly considered that data reported from the PREDICTIVE observational study was at variance with the Levemir summary of product characteristics (SPC).

PREDICTIVE was a multinational, non-interventional, uncontrolled observational study designed to evaluate the incidence of serious adverse reactions, including major hypoglycaemic events, during Levemir treatment over 12, 26 or 52 weeks in type 1 or type 2 diabetics. The study involved 30,000 adults and children. The data included in the advertisement was a subanalysis of a defined cohort of European patients with type 2 diabetes, who were insulin naïve, initiated on Levemir and followed for 12 weeks (n=1,798).

The advertisement made a number of claims derived from the PREDICTIVE study. Firstly, it was claimed that '… the initiation of Levemir is effective for patients with type 2 diabetes, without increasing the risk of hypoglycaemia'. Lilly alleged that in the absence of an active comparator such a conclusion could not be substantiated and was misleading in breach of Clause 7.4.

It was also claimed that 'the number of major hypoglycaemic events were significantly reduced for both daytime (p=0.021) and all (p=0.013)'. Again, in the absence of an active comparator, such a conclusion could not be substantiated and was misleading, potentially compromising patient safety. The Levemir SPC stated 'Hypoglycaemia is a common undesirable effect. It may occur if the insulin dose is too high in relation to the insulin requirement. From clinical investigations it is known that major hypoglycaemia, defined as requirement for third party intervention, occurs in approximately 6% of patients treated with Levemir. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death'.

Hypoglycaemia was a significant and potential life-threatening side effect of insulin therapy and despite being listed in the Levemir SPC as common, nowhere in the item had the risk with Levemir been highlighted to readers and incidence data were not included. Lilly alleged that the advertisement was thus not in accordance with the terms of the Levemir marketing authorization and was inconsistent with the particulars listed in the Levemir SPC in breach of Clause 3.2.

Secondly, it was claimed that there were 'Weight advantages with Levemir'. This claim was also at variance with the Levemir SPC which stated that 'Studies in patients with type 2 diabetes treated with basal insulin in combination with oral antidiabetic drugs demonstrates that glycaemic control (HbA1c) with Levemir is comparable to NPH insulin and insulin glargine and associated with less weight gain'. However, weight gain ranging from 0.7kg to 3.7kg was associated with Levemir treatment, varying with dosing and duration of treatment.

This was an uncontrolled observational study, and any findings in patients who had initiated Levemir would be confounded by a number of other factors including changes in other diabetes medicines and any lifestyle interventions which might be instituted as part of clinical practice. It was not possible to extrapolate from this data that any reported weight advantages were attributable to Levemir. Therefore the claim 'weight advantages with Levemir' was not capable of substantiation. Breaches of Clauses 7.2 and 7.4 were alleged.

Lilly submitted that the weight data, as presented, were very difficult to interpret. In the advertisement it had been stated that 52% of patients lost weight. This had been further detailed as follows: 43%, 26.3% and 15.6% of patients lost 1, 2 or 3kg respectively. This was followed by the statement: 'Of those reviewed over half lost an average of more than 2.5kg in weight in only 12 weeks'. Within this advertisement feature it was very difficult to reconcile these figures and in Lilly's view it was ambiguous in breach of Clause 7.2.

Lilly alleged that the undue emphasis placed on weight change within the advertisement, as evidenced by the large graph, was misleading. Weight change was not the primary objective of the study and indeed could be self-reported by patients, contributing to substantial bias. Therefore any claims of weight change derived from this study were misleading.

The advertisement was designed to resemble an editorial written independently by a respected peer. Sponsorship of this advertisement had not been declared, in breach of Clause 9.10. It was also Lilly's view that this represented disguised promotion, in breach of Clause 10.1 of the Code.

Pulse was the UK's leading medical weekly, counting 80% of GPs among its regular readers. Therefore, this misleading advertisement had been widely disseminated, disguised as a review by a respected peer. It potentially misled health professionals and in particular might compromise patient safety. In Lilly's view this brought discredit to, and reduced confidence in, the pharmaceutical industry (Clause 2).

Lilly asked Novo Nordisk to immediately stop using claims from the PREDICTIVE observational study without appropriate qualification, clearly detailing the limitations of the study design. All claims should be consistent with the SPC. In addition, Lilly asked Novo Nordisk, in an effort to redress that miscommunication, to issue a corrective statement of equal prominence in Pulse acknowledging the issues as set out above.

RESPONSE

Novo Nordisk noted that Lilly's primary concern related to the alleged lack of a declaration of sponsorship on the advertisement (Clause 9.10), and disguised promotion (Clause 10.1). Novo Nordisk believed that it was clear to the reader that the material was an advertisement for Levemir and two different Novo Nordisk insulin devices because: both pages were headed 'Advertisement Feature'; Levemir prescribing information had been included; adverse event reporting was requested to be made to Novo Nordisk and the two pages featured large pictures of Levemir-related insulin devices. Novo Nordisk did not see how someone could interpret this advertisement as an independent review. Pulse regularly featured advertorial pieces of this style and its readers would be sufficiently accustomed to their promotional nature. Novo Nordisk denied breaches of Clauses 9.10 and 10.1 of the Code.

The PREDICTIVE observational trial was a multinational, non-interventional, uncontrolled and observational study designed to evaluate the real-life safety and efficacy of Levemir in day-to-day clinical practice. Novo Nordisk's primary aim was to reveal any safety or efficacy concerns which would contradict the findings from its extensive randomized clinical trial programme; the PREDICTIVE data analyzed so far had confirmed the favourable results from the randomized clinical trials Novo Nordisk had conducted with Levemir (Dornhorst *et al*, 2007). Novo Nordisk would never promote any results from an uncontrolled observational trial which contradicted the existing data from trials of a higher level of evidence.

Risk of hypoglycaemia with insulin detemir

Lilly had alleged that the claim of '… the initiation of Levemir is effective for patients with type 2 diabetes, without increasing the risk of hypoglycaemia' could not be substantiated due to the lack of an active comparator in the trial.

The trial did have a comparator period which was precisely defined regarding hypoglycaemic events. Patients were asked to report the number of hypoglycaemic events during the four weeks preceding the initiation of Levemir (baseline visit). The hypoglycaemic event rate during the period was compared to the rate during the last four weeks of the observation period, before the final visit. One could argue about potential recall bias, however Novo Nordisk believed that every patient who had had a major hypoglycaemic event (requiring third party intervention) in the recent past would be able to recall it. Since major hypoglycaemic events had a significant risk reduction when compared to the risk with previous treatment, Novo Nordisk believed that this claim could be substantiated with the results from this subgroup of PREDICTIVE. Lilly also emphasized its concern regarding the contradiction between these data and a statement from the Levemir SPC. Novo Nordisk noted that the major hypoglycaemic event rate in the SPC was primarily derived from randomized clinical trials conducted in type 1 diabetes. In these trials Levemir was used as part of basal-bolus therapy. Since type 1 diabetes was related to much higher rates of hypoglycaemic events, it was difficult to interpret this statement to an insulin-naïve subgroup of type 2 diabetics using basal+oral therapies.

Furthermore, Novo Nordisk provided data on major hypoglycaemic event rates (24 hour) from its randomized clinical trials conducted in insulin-naïve type 2 diabetics after initiation of Levemir. These trials compared the hypoglycaemic risk of Levemir with the hypoglycaemic risk of NPH or Lantus. Baseline characteristics of patients in these trials were comparable with those in the subgroup of PREDICTIVE.

- Comparison of once-daily Levemir with NPH insulin added to a regimen of oral antidiabetic medicines in poorly controlled type 2 diabetes (Philis-Tsimikas *et al*)
  - o Major hypoglycaemic events with Levemir injected in the evening: 2 events/20 weeks (0.03 event/patient year)
  - o Major hypoglycaemic events with Levemir injected in the morning: 0 events/20 weeks
  - o Major hypoglycaemic events with NPH insulin injected in the evening: 0 events/20 weeks.

- A 26-week, randomized, parallel, treat-to-target trial compared Levemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naïve type 2 diabetics (Hermansen *et al*, 2006)
  - o Major hypoglycaemic events with Levemir: 1 event/21 weeks (0.01 event/patient year)
  - o Major hypoglycaemic events with NPH insulin: 8 event/24 weeks (0.08 event/patient year)

- Levemir vs Lantus as add-on to current oral antidiabetic therapy in insulin-naïve type 2 diabetics (Rosenstock *et al*, 2006)
  - o Major hypoglycaemic events with Levemir: 9 events/52 weeks (0.03 event/patient year)
  - o Major hypoglycaemic events with Lantus 8 events/52 weeks (0.03 event/patient year).

The major hypoglycaemic event analysis of the PREDICTIVE subgroup revealed a patient/year event rate of less than 0.01, which seemed to be better than findings from the randomized clinical trials.

The significant risk reduction Novo Nordisk observed during the observational period (compared to the baseline event rate with previous oral antidiabetic therapy alone) could not be compared with any data from its randomized clinical trial due to the lack of hypoglycaemic data before randomization in the above studies. However, there were reliable data on major hypoglycaemic event rates with oral antidiabetic therapy in type 2 diabetes. This rate was typically between 0.009 and 0.028 event/patient year (Leese *et al*, 2003, Shorr *et al*, 1997) which might explain the significant risk reduction of major hypoglycaemic events in PREDICTIVE. Furthermore a recently published comprehensive review about hypoglycaemia in type 2 diabetes (Zammitt and Frier, 2005) also referred to the authors' own experience with basal+oral regimen and reported no major hypoglycaemic events following insulin initiation.

With regard to all hypoglycaemic event rates observed in Novo Nordisk's trial, it agreed with the potential criticism that the rate was underestimated due to recall bias. However such recall bias would also be relevant in the case of recalling the prestudy event rate (with oral antidiabetic therapy alone). Therefore this kind of bias did not have any impact on the interpretation of the results comparing the two periods. On this basis, Novo Nordisk believed the claim could be substantiated from the PREDICTIVE study and confirmed the findings of the major hypoglycaemic event rates revealed in its clinical trials referred to above. Therefore Novo Nordisk could not accept the argument that these hypoglycaemia results would not be valid and rejected Lilly's allegations that health professionals had been misled and patient safety compromised.

In the recently published European Association for the Study of Diabetes/American Diabetes Association (EASD/ADA) guideline for the management of hyperglycaemia in type 2 diabetes, the authors highlighted that in different treat-to-target clinical trials the observed frequencies of severe hypoglycaemic episodes in type 2 diabetes were between 1 and 3 events/100 patient-years (Nathan *et al*, 2006). This rate was comparable with the frequency detected in the PREDICTIVE study (0.01 event/patient-year). Novo Nordisk submitted that health professionals knew that there was a risk of hypoglycaemia in any case of insulin treatment. This advertisement did not conflict with such practical experience, but provided reliable data on the frequency of major hypoglycaemic events to be expected after insulin initiation with Levemir.

Novo Nordisk noted that the advertisement contained results not only from its PREDICTIVE observational trial, but also from a randomised clinical trial in a comparable patient population. The findings on major hypoglycaemic events from this trial (Philis-Tsimikas *et al*) were very similar to the findings in the PREDICTIVE study. Lilly repeatedly referred to that part of the Levemir SPC which stated that the average frequency of major hypoglycaemic events was 6%. Novo Nordisk noted that this event rate came from randomized clinical trials conducted in type 1 diabetes, when Levemir was used as part of basal-bolus therapy. Since it was beyond any question that type 1 diabetes related to a much higher frequency of hypoglycaemic events, omitting such differences between basal-bolus and basal+oral therapies (Diabetes Control and Complications Trial Research Group, 1993), rendered the comparison between the hypoglycaemic event rate from the PREDICTIVE study (the subject of this piece) and the rate from the SPC incongruous. Therefore Novo Nordisk did not believe that the content of the advertisement about major hypoglycaemic events would mislead the relevant patient population or compromised patient safety.

Weight benefit of Levemir

Novo Nordisk strongly agreed that weight findings from an uncontrolled observational trial should be interpreted with caution if they contradicted findings from clinical trials of a higher level of evidence. However, this weight benefit was a consistent finding in all Novo Nordisk randomized clinical trails when Levemir was compared with other basal insulins regardless of the type of diabetes or the applied insulin regimen (Russell-Jones *et al*, 2004, Pieber *et al*, 2005, Home *et al*, 2004, Hermansen *et al*, 2004, Raslova *et al*, 2004, Haak *et al*, 2005, Robertson *et al*, 2007, Philis-Tsimikas *et al*, Hermansen *et al*, 2006, and Rosenstock *et al*). The only exception was a trial that compared Levemir with Lantus in type 1 diabetes as part of basal bolus therapy where the average weight gains were 0.52kg (Levemir) and 0.96kg (Lantus) with no statistically significant difference between the two (Pieber *et al*, 2007). In the following trials patients randomized to Levemir experienced:

- less average weight gain than patients with the comparator (Home *et al*,– $Idet_{morn+bed}$, Raslova *et al*, Haak *et al*, Philis-Tsimikas *et al*, Hermansen *et al*, 2006, Rosenstock *et al*) or
- weight neutrality (Home *et al*, – $Idet_{12\text{-}hour}$, Pieber *et al*, 2005 – $Idet_{morn+bed}$) or, an
- average weight loss when compared with patients on the comparator arm (Russell-Jones *et al*, Pieber *et al*, 2005 – $Idet_{morn+din}$, Hermansen *et al*, 2004).

Since insulin initiation in type 2 diabetes had been related to weight gain Novo Nordisk believed this finding from the PREDICTIVE trial should be shared with its customers. In the PREDICTIVE trial the weight benefit was revealed not only in this subgroup of type 2 diabetics, but also in type 2 patients switched from premix insulin preparations to Levemir and in users of a basal bolus regimen (both in type 1 and 2) when they were switched to Levemir from either NPH insulin or Lantus. Novo Nordisk did not know of any other insulin which could provide such consistent weight findings as Levemir.

Novo Nordisk believed it was difficult to interpret this weight benefit from all the above mentioned clinical trials other than to a phenomenon linked to the use of Levemir. There could be confounders in an observational trial which made it harder to interpret the results. However Novo Nordisk did not know of any potential confounder that would affect patients' weight consistently and favourably, regardless of the type of diabetes and the type of applied insulin regimen.

Lilly had specified weight data from the Levemir SPC (0.7kg and 3.7kg). Novo Nordisk noted that this was from two different randomized clinical trials using a different number of basal insulin injections, over different trial periods. The PREDICTIVE subgroup analysed in this advertisement were those patients who were uncontrolled on oral antidiabetic therapy alone prior to PREDICTIVE and who entered PREDICTIVE on once daily Levemir and were followed for 12 weeks. This subgroup of patients mirrored those in Philis-Tsimikas *et al* except in this clinical trial oral antidiabetic therapy remained unchanged from randomization. This was why a table showing the change of oral antidiabetic therapy was included which Novo Nordisk was sure was one of Lilly's concerns regarding the weight changes in PREDICTIVE.

In the advertisement Novo Nordisk had clearly specified that the weight loss of 0.6kg was the mean for the whole

subgroup and highlighted the percentages of patients who gained weight (32%), remained the same weight (16%) and lost weight (52%) on average. Therefore Novo Nordisk rejected the allegation that the information on weight changes observed in this subgroup of patients from the PREDICTIVE trial could not be substantiated and potentially misled health professionals.

Novo Nordisk submitted that nothing in the advertisement suggested that Levemir had a weight sparing effect. Apart from providing the weight findings for the readers, the summary clearly stated no more than 'heavier patients experienced a greater weight loss' during the observational period. This had also been reported in Novo Nordisk's randomized clinical trials (Hermansen *et al*, 2006). Furthermore, it would be seen from the article that data from PREDICTIVE was balanced with data from a randomized clinical trial (Philis-Tsimikas *et al*).

Although Novo Nordisk agreed that the detailed weight data giving the percentages of patients losing 1, 2 or 3kg of weight during the observational period could have been written more clearly, it did not mislead. The figures relating to the categories of average weight loss represented cumulative percentages. Despite not being straightforward, this information could be interpreted with common sense. It was difficult to make any other interpretation than this, since the paragraph above clearly stated the proportion of patients who lost, remained the same or gained weight during the study.

Novo Nordisk believed that the rising incidence of obesity, and hence type 2 diabetes, was one of the major challenges faced in healthcare. Thus every kind of antidiabetes medicine, having proven favourable effect on weight or preventing further weight gain when compared to other existing therapeutic modalities, should be communicated to the relevant health professionals.

Findings from the PREDICTIVE study had been shared with Novo Nordisk's customers so far in three different publications in peer-reviewed scientific journals (Meneghini *et al*, 2007, Lüdekke *et al* and Dornhorst *et al*). Since the launch of the trial, different aspects of the results had been presented 44 times at highly credible international scientific meetings and reflected the quality of data from PREDICTIVE. Low quality data would not have been so widely accepted.

Therefore Novo Nordisk had a clear intention to share the important findings of one of the largest observational trials ever conducted in diabetes, with health professionals. Any promotional piece containing information from the PREDICTIVE study also provided sufficient information for the readers to decide how the results should be interpreted. Novo Nordisk did not consider that it needed to emphasise the weaknesses of observational trials in general (given the fact that at least a short description of the trial was included in all of its materials). Novo Nordisk believed health professionals had the necessary epidemiological knowledge to allow them to make their own conclusions.

PANEL RULING

The Panel noted that the advertisement had appeared in Pulse. Although the material was presented in the style of an advertorial the Panel did not consider that it resembled normal editorial material in Pulse. It was clearly headed 'Advertisement Feature'. The highlighting in the advertisement was all in green whereas highlighted text in Pulse was always in shades of blue. The Panel considered that the layout and presentation of the advertisement was such that readers would not be misled as to its promotional nature. Prescribing information was included. The Panel thus did not consider that the advertisement was disguised promotion and so no breach of Clause 10.1 was ruled. As the piece was clearly an advertisement no declaration of sponsorship was required. Prescribing information was clearly provided and so readers would know that the advertisement had been produced by Novo Nordisk. No breach of Clause 9.10 was ruled.

The Panel noted that the advertisement included a section describing the PREDICTIVE study. The claim 'This suggests that the initiation of Levemir is effective for patients with type 2 diabetes, without increasing the risk of hypoglycaemia' was not a stand alone claim; it came at the end of a block of text which discussed the 12 week data from a subgroup of the PREDICTIVE study (Novo Nordisk data on file). Previous text described the subgroup patient population ie type 2 diabetics who, at baseline were insulin-naïve and uncontrolled on oral anti-diabetic medicine. The data on file showed that adding Levemir to the existing oral therapy did not increase the risk of hypoglycaemia compared to baseline. In that regard the Panel considered that, given the context in which the claim appeared, it was clear that the comparison was with baseline ie oral antidiabetic therapy alone, and so in that regard the claim could be substantiated. The absence of an active comparator in this context did not mean that the claim could not be substantiated as alleged. No breach of Clause 7.4 was ruled.

Similarly the claim 'The number of major hypoglycaemic events were significantly reduced for both daytime ($p=0.021$) and all ($p=0.013$)' was not a stand alone claim but part of the text describing the PREDICTIVE study subgroup data. However the Panel noted that Lilly had not cited a clause as required by Paragraph 5.2 of the Constitution and Procedure and thus made no ruling on this point.

The Panel considered that prescribers would be well aware that insulin therapy was associated with a risk of hypoglycaemia. The advertisement at issue examined the incidence of major hypoglycaemic episodes in type 2 diabetics before and after the addition of Levemir to their existing oral therapy and reported a reduced number. The advertisement did not state or imply that there was no risk of hypoglycaemia with Levemir therapy. In that regard, and given the audience to whom it was directed, the Panel did not consider that the advertisement was inconsistent with the particulars listed in the Levemir SPC. No breach of Clause 3.2 was ruled.

The claim 'Weight advantages with Levemir' was a

stand alone claim as it appeared as the heading to a section of text discussing the results from the PREDICTIVE study subgroup data for type 2 diabetics. The associated text referred to a mean decrease in weight of 0.6kg from baseline to week 12 in type 2 diabetics. It was further explained that during the study 52% of patients lost weight, 16% maintained the same weight and 32% had an increase in weight. A prominent bar chart depicted the results and in that regard emphasised the weight loss observed in the PREDICTIVE type 2 diabetes subgroup.

The Panel noted that the Levemir SPC stated that in studies in type 2 diabetes, patients treated with Levemir plus oral antidiabetic medicines gained less weight than those treated with Lantus plus oral antidiabetic medicines.

The Panel considered that with regard to changes to be expected in body weight, the advertisement was inconsistent with the Levemir SPC. In the Panel's view the advertisement implied that, in general, patients lost weight when Levemir was initiated whereas the SPC stated that they gained weight, albeit less than with other insulins. The Panel considered that although the advertisement reported the findings of the PREDICTIVE study, such findings were inconsistent with the particulars listed in the SPC. A breach of Clause 3.2 was ruled. The Panel further considered that, in general, the claim 'Weight advantages with Levemir' was thus misleading and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled. These rulings were appealed.

The Panel considered that the detailed weight data, as presented, was difficult to interpret as alleged. The percentages of patients losing 1,2 or 3kg were cumulative not absolute although this was not explained, thus it appeared that 15.6% of patients lost 3kg of weight, 26.3% lost 2kg of weight and 43% lost 1kg of weight which was not so. In that regard the Panel considered that the advertisement was misleading and ambiguous. A breach of Clause 7.2 of the Code was ruled. The Panel noted that Novo Nordisk had acknowledged that this part of the advertisement could have been written more clearly.

Overall the Panel did not consider either generally or in relation to the hypoglycaemic data, that the advertisement warranted a ruling of a breach of Clause 2 of the Code which was reserved as a sign of particular censure. No breach of Clause 2 was thus ruled in relation to each matter.

APPEAL BY NOVO NORDISK

Novo Nordisk submitted that in terms of the inconsistency with the Levemir SPC, it noted that the regulatory authorities considered all the then available evidence when they granted permission to use Levemir in combination with oral antidiabetics. When Novo Nordisk submitted all the available evidence in October 2006 to the European Medicines Agency (EMEA), only a fraction of the results from the PREDICTIVE trial were available and there was no full peer-reviewed publication from the study. Therefore, there was no opportunity to provide them with the robust and convincing results from the largest observational study ever conducted in the field of insulin treatment in diabetes mellitus. During the last twelve months four clinical papers (Dornhorst *et al*, Ludekke *et al*, Meneghini *et al*, 2007/May, and Meneghini *et al*, 2007/November) were published in peer-reviewed journals; three of which analysed weight as a secondary outcome of the study (the fourth publication analysed baseline patient characteristics and predictors of hypoglycaemic events).

1 In Dornhorst *et al*, data of 20,531 patients with type 1 or type 2 diabetes were analysed. Weight decreased from baseline significantly by -0.1kg ($p<0.01$) and -0.4kg ($p<0.0001$) in type 1 and type 2 diabetes, respectively.

2 In insulin-naïve patients with type 2 diabetes (n=1321) from the German cohort of the PREDICTIVE trial analysed in Menghini *et al*, May, an average weight loss of -0.9kg was detected ($p<0.0001$). A similar weight reduction was found in patients who were switched to Levemir±OADs from NPH±OADs (-0.9kg, $p<0.0001$, n=251) or Lantus±OADs (-0.8kg, $p<0.0001$, n=260).

3 In the most recent publication Meneghini *et al*, November, which compared two different Levemir titration approaches in a randomized way, +1.1kg weight gain was observed in one arm of the trial whilst in the other arm +0.4kg weight gain was revealed (statistical comparison was made to detect any difference in the weight change between the two arms ($p=0.0314$)). These weight changes were found in the subcohort of patients with type 2 diabetes who were insulin-naïve at baseline.

Furthermore, Novo Nordisk noted that investigators of PREDICTIVE communicated the results in 28 oral or poster presentations on international diabetes meetings (IDF 2006, Cape Town, South-Africa; ADA 2007 Chicago and EASD 2007 Amsterdam). Novo Nordisk highlighted the weight findings from some published abstracts from these meetings:

IDF 2006

1 Aczel *et al* (abstract 119): weight reduction of 0.2kg was found both in type 1 (n=2426) and in type 2 (n=1610) diabetes ($p<0.001$ and $p<0.01$, respectively).

2 Ludekke *et al* (abstract 380): in n=6364 patients with type 1 diabetes an average weight reduction of 0.2kg ($p<0.001$) was observed whilst in type 2 diabetes (n=11901) a reduction of 0.5kg ($p<0.001$) was revealed.

3 King *et al* (abstract 921): in 306 patients with type 2 diabetes who were switched from either NPH or Lantus plus OADs to Lantus plus OADs, a weight reduction of 0.5 kg ($p<0.05$) was observed.

4 Sreenan *et al* (abstract 388): data of n=1583 patients with type 1 diabetes and n=743 patients with type 2 diabetes were analysed. These patients were treated with a basal-bolus insulin regimen. The basal part (Lantus) of the regimen was switched to Levemir at baseline. Investigators observed a weight reduction of 0.4kg and 0.5kg in type 1 and type 2 diabetes, respectively ($p<0.001$ in both cases).

5 Dornhorst *et al* (abstract 370): investigators found an average weight reduction of 0.7kg in 2314 patients with insulin-naïve type 2 diabetes when Levemir was introduced as initial insulin therapy (p<0.001).

ADA 2007

6 Sreenan *et al* (abstract 549-P): the weight change was analyzed in different subgroups of insulin-naïve patients with type 2 diabetes after Levemir initiation. When Levemir was combined with metformin+sulfonylurea (n=269) they observed a weight reduction of 0.4kg (p=NS). When sulfonylurea was discontinued and Levemir was used in combination with metformin (n=161) the weight reduction was 1.7kg (p<0.0001). In terms of combination of Levemir with thiazolodendione (TZD) (n=95), a weight gain of 0.3kg was found (p=NS), whilst in case of discontinuation of TZD (n=202) a weight reduction of 0.8kg was revealed (p<0.0115).

7 Gallwitz *et al* (abstract 550-P): patients initiated with once-daily Levemir in the morning (n=351) or evening (n=1,693) were compared in this analysis. In patients who injected Levemir in the morning, a non-significant weight loss of 0.3kg was observed, whilst those patients with an evening injection showed a significant weight reduction of 0.7kg (p<0.0001).

8 Dornhorst *et al* (abstract 2196-PO): investigators analysed weight change after initiation with Levemir or switching from another insulin to Levemir in 748 elderly patients (age≥65yrs) with type 2 diabetes. In patients who were insulin-naïve at baseline a weight reduction of 0.3kg was observed (p=NS), whilst in patients who were switched to Levemir from another insulin preparation a weight loss of 0.5kg was found (p<0.0001).

Novo Nordisk submitted that instead of making this comprehensive list of presentations from the PREDICTIVE trial even longer (Novo Nordisk provided a detailed list of the abstracts), it noted why it believed that these findings should be shared with health professionals. Inevitably, being overweight or obese were major public health problems which led to the development of several metabolic disorders such as insulin resistance and type 2 diabetes. They were not only risk factors which played important roles in the development of glucose intolerance but also co-morbidities which had major impact on the success of treating hyperglycaemia. In fact the recently published ADA/EASD treatment guideline emphasised that 'promoting weight loss or at least avoiding weight gain should remain an underlying theme throughout the management of type 2 diabetes, even after medications are used' (Nathan *et al*, 2006).

Novo Nordisk submitted that the above mentioned publications and abstracts from the PREDICTIVE trial further confirmed the important and consistent findings from the randomized clinical trials that Levemir had a weight advantage when compared to other basal insulin preparations. Bearing in mind that the PREDICTIVE results were not available when the EMEA made the last modification to the Levemir SPC, important findings from this large (>30,000 patients with diabetes), multinational (>20 countries), observational study should be shared with health professionals. It was generally acknowledged that observational studies might provide important and clinically relevant information which could not be fully revealed by smaller sized randomized clinical trials. Results from observational studies might be equally or even more relevant for clinical practice since they came from clinical practise itself. No one would deny that findings from an observational study should be handled carefully due to potential confounding factors. However, it remained that the weight advantage of Levemir as shown in the PREDICTIVE study was observed in patients with type 1 and type 2 diabetes, regardless of whether they were insulin-naïve or not. One potential confounding factor could, of course, be structured lifestyle education at the time of insulin initiation. However, such a consistent finding would not be a consequence of such education. The only one consistent therapeutic step in PREDICTIVE was to introduce Levemir, not an educational programme. Undoubtedly, the method of education, its intensity and content would be different in different countries and in different patient groups.

Novo Nordisk submitted that it had never promoted Levemir as a weight reducing medicine. This would, of course, be totally unacceptable in the case of any insulin preparation. Novo Nordisk was well aware of the difference of promoting an anti-obesity medicine and an insulin preparation that had shown a weight benefit. There was a huge difference in sharing the latest findings from a robust observational study or promoting it as a weight sparing medicine. This was precisely why the findings from PREDICTIVE were reported alongside those of a randomised clinical trial, in the advertisement.

In regard to the claim of 'Weight advantages with Levemir', Novo Nordisk submitted that claiming a 'weight advantage' had not meant the same as stating that the use of a product would result in weight loss. From all the evidence available a feature of Levemir, possibly due to its different mode of action, had an impact on weight gain that was not shown with other basal insulin preparations. This was the message that Novo Nordisk was endeavouring to communicate with this claim. Clearly, it was an advantage to use insulin that was associated with significantly less weight gain (type 2 insulin initiation) or no weight gain (type 1, basal bolus regimen), compared to other available basal insulin preparations, that were not associated with the same advantage.

Novo Nordisk submitted that weight management was an integral part of diabetes therapy, therefore finding such an advantage of an insulin preparation was an important one, which should be shared with health professionals. However, sharing this observation from an uncontrolled observational study (even if it was the largest ever conducted study in the field of insulin treatment and diabetes) would not be appropriate without providing the evidence along side randomized controlled trials. That was why the advertisement covered the findings from the PREDICTIVE trial and also from an important randomized clinical trial (Philis-Tsimikas *et al*, 2006) in order to provide 'accurate, balanced, fair, objective and unambiguous information' which was relevant for primary care physicians when

they started insulin treatment in type 2 diabetes. The two page advertisement clearly demonstrated this.

Novo Nordisk submitted that one interesting result relating to the weight change during the course of this randomized clinical trial was a trend for those people with the highest body mass index (BMI) at baseline to gain less weight compared to those with smaller BMI measures (Philis-Tsimikas *et al*, 2007).

Novo Nordisk submitted that the similar trend of weight change, with increasing baseline BMI, was also found in the subgroup analysis reported in the advertisement. At the time of the advertisement, the above analysis was not available otherwise it would have also been included. For these reasons, Novo Nordisk did not agree with the ruling of the Panel that the advertisement breached Clauses 7.2 and 7.4 of the Code.

COMMENTS FROM LILLY

Lilly noted that the promotion of a medicine must be in accordance with the terms of its marketing authorisation. In order for the PREDICTIVE data to be included in the SPC, a variation needed to be submitted to the European regulatory authorities for approval. This approval was not reflected in the current Levemir SPC. Lilly alleged that within the advertisement, weight 'advantages' with Levemir were reported as weight loss for 52% of patients, with 32% gaining weight. A prominent bar chart emphasised the weight loss observed in the study. Therefore, Novo Nordisk's claim that there were 'Weight advantages with Levemir' was at variance with the Levemir SPC which stated that 'Studies in patients with type 2 diabetes treated with basal insulin in combination with oral antidiabetic drugs demonstrates that glycaemic control (HbA1c) with Levemir is comparable to NPH insulin and Lantus and associated with less weight gain'. However, weight gain ranging from 0.7kg to 3.7kg was associated with Levemir treatment, varying with dosing and duration of treatment. Therefore, Lilly agreed with the Panel's ruling of a breach of Clause 3.2 in this regard.

Breach of Clauses 7.2 and 7.4

Lilly noted that PREDICTIVE was a multinational, non-interventional, uncontrolled observational study designed to evaluate the incidence of serious adverse drug reactions, including major hypoglycaemic events, during Levemir treatment over 12, 26 or 52 weeks in patients with both type 1 and type 2 diabetes. Lilly alleged that as this was an uncontrolled observational study, any findings in patients who had initiated Levemir were likely to be confounded by a number of other factors. These might include changes in other diabetes medications and any lifestyle interventions instituted as part of clinical practice. It was therefore not possible to extrapolate from this data that any reported weight 'advantages' were solely attributable to Levemir.

Lilly alleged that the advertisement implied that in general, patients lost weight with Levemir. It was not possible to extrapolate from this data that any reported weight advantages were attributable to Levemir. Therefore the claim 'Weight advantages with Levemir' could not be substantiated. In order to comply with the Code as laid out in Clauses 7.2 and 7.4 'Information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must be based on up-to-date evaluation of all the evidence and reflect the evidence clearly. They must not mislead either directly or by implication, by distortion, exaggeration or undue emphasis. Materials must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine' and 'Any information, claim or comparison must be capable of substantiation'. The weight data, as presented, were very difficult to interpret. In the advertisement feature it had been stated that 52% of patients lost weight. Further percentage of patients losing 1, 2 or 3kg was 43%, 26.3%, and respectively 15.6%. Lilly alleged that these results were cumulative, not absolute. In general, the claim 'Weight advantages with Levemir' was misleading and ambiguous and incapable of substantiation. Lilly therefore agreed with the Panel's ruling of a breach of Clauses 7.2 and 7.4.

Lilly submitted that the undue emphasis placed on weight loss within the advertisement, as evidenced by the large graph, was misleading. Weight loss was not the primary objective of the study and indeed weight could be self-reported by patients in the study, contributing to substantial bias. Therefore any claims of weight loss derived from this study were misleading to Novo Nordisk had stated that weight advantage had not meant the same as weight loss. While this might be correct, the data used to support this claim suggested that there would generally be weight loss associated with Levemir therapy. This was clearly at variance with the Levemir SPC and was misleading. Novo Nordisk also stated that weight management was an integral part of diabetes therapy. It was for this reason that it was impossible to extrapolate the suggested benefits of weight loss from this study design. The lack of a comparator within this study made any claims of weight advantage incapable of substantiation. Novo Nordisk also stated that it had never promoted Levemir as a weight loss medicine. However a recent advertisement highlighting that 'Levemir is changing figures' had recently been ruled in breach of the Code as being misleading, suggesting that Levemir treatment would result in weight loss. This decision was upheld on appeal.

Whilst Lilly supported the use of large observational studies to support the important primary endpoint of safety, the use of these studies to make other promotional claims should be done with caution and should be aligned with the SPC.

APPEAL BOARD RULING

The Appeal Board noted that the PREDICTIVE study was a prospective, observational, uncontrolled study designed to assess the safety and efficacy of Levemir in routine clinical practice in type 1 and type 2 diabetes. The claim 'Weight advantages with Levemir' appeared as the heading to a section of text discussing the results from the subgroup of insulin-naïve type 2 diabetics, uncontrolled on oral therapy (n=1,798). The associated text referred to a mean decrease in weight of 0.6kg from baseline to week 12. It was further explained that during the study 52% of patients lost weight, 16% maintained

the same weight and 32% had an increase in weight. A prominent bar chart depicted the mean weight change by BMI in type 2 diabetics initiated on Levemir. The advertisement also stated that 'of those patients reviewed (n=1,525) over half lost an average of more than 2.5kg in weight in only 12 weeks'. The Appeal Board did not consider that this was consistent with the figures provided for the percentage of patients losing 1kg (43%), 2kg (26.3%) or 3kg (15.6%) as ruled upon separately by the Panel.

The Appeal Board noted that the Levemir SPC stated that in studies in type 2 diabetes, patients treated with Levemir plus oral antidiabetic medicines gained less weight than those treated with Lantus plus oral antidiabetic medicines. The Appeal Board noted that the studies cited in the SPC were of 20 – 52 weeks' duration.

The Appeal Board noted a number of confounding factors in the PREDICTIVE study. In particular the use of sulphonylureas and glitazones, both of which were associated with weight gain, had decreased by the end of the study thus the observed weight loss might not have been entirely attributable to Levemir. It was further noted that weight could be self-reported by patients which in the Appeal Board's view might bias results towards weight loss rather than weight gain. In addition some patients, as a result of being observed, might have introduced lifestyle changes which might have had a beneficial effect on weight.

The Appeal Board considered that with regard to changes to be expected in body weight, the advertisement was inconsistent with the Levemir SPC and had not presented the balance of the evidence. In the Appeal Board's view the advertisement implied that, in general, patients lost weight when Levemir was initiated whereas the SPC stated that they gained weight, albeit less than with other insulins. The Appeal Board considered that although the advertisement reported their findings of the PREDICTIVE study, such findings were inconsistent with the particulars listed in the SPC. The Appeal Board upheld the Panel's ruling of a breach of Clause 3.2. The appeal on this point was unsuccessful. The Appeal Board further considered that, given the points discussed above the claim 'Weight advantages with Levemir' was thus misleading and could not be substantiated. The Appeal Board upheld the Panel's ruling of breaches of Clauses 7.2 and 7.4. The appeal on this point was unsuccessful.

Complaint received	**12 September 2007**
Case completed	**5 February 2008**