CASE AUTH/2273/10/09

# LILLY v NOVO NORDISK

## Victoza launch

**Lilly complained about promotional and press materials issued to mark the launch of Victoza (liraglutide) by Novo Nordisk. Allegations were also made about patient support materials. Lilly made many repetitive allegations and they are not all repeated in this summary. The detailed complaint from Lilly is given below.**

**Victoza was a once daily, human glucagon-like peptide (GLP)-1 analogue. It was indicated for the treatment of type 2 diabetes to achieve glycaemic control firstly in combination with metformin or a sulphonylurea in patients with insufficient glycaemic control despite maximally tolerated dose of monotherapy with metformin or a sulphonylurea. Secondly in combination with metformin and a sulphonylurea or a thiazoldinedione in patients with insufficient glycaemic control despite dual therapy. Byetta (exenatide), was a twice daily GLP-1 analogue, marketed by Lilly, licensed for second-line use with sulphonylureas or metformin.**

**With regard to public relations materials Lilly referred to seven articles (including one television and one radio interview) in the lay and health professional media. Lilly was concerned that the articles implied that Victoza was to be used for weight loss or reductions in blood pressure (BP) rather than its licensed indication. Lilly alleged that the overwhelming emphasis on weight reduction was likely to raise unfounded hopes of successful treatment. The same could be said of the implied claim of protection against heart disease by virtue of Victoza's effect on BP. Lilly alleged breaches of many clauses of the Code including a failure to provide details of precautions and side effects.**

**The detailed response from Novo Nordisk is given below.**

**In considering the allegations about articles/interviews in the media the Panel examined the press materials provided by Novo Nordisk, not the articles/interviews per se. The media backgrounder package comprised seven documents including one on 'Incretins' and another on 'Victoza (liraglutide)'. There was also a lay press release and a medical press release. The Panel considered that as the press pack did not include details of precautions or side effects it was likely to mislead as to the overall benefits of Victoza. Breaches of the Code were ruled.**

**The Panel was concerned that the overall impression of the press pack was that Victoza was to be prescribed to control blood glucose, reduce weight, reduce BP and improve β-cell function. The materials were not clear regarding the licensed indication as set out in the summary of product characteristics (SPC). The press pack placed equal emphasis on the pharmacodynamic information set out in the SPC with regard to reductions in weight and BP and improved β-cell function. Readers might be confused as to the precise indication for Victoza. Little mention was made that Victoza was only to be prescribed as combination therapy when first and/or second line oral treatment failed to produce adequate glycaemic control.**

**The Panel ruled that the backgrounders 'Incretins' and 'Victoza (liraglutide)' were misleading with regard to the licensed indication and inconsistent with the SPC. On appeal by Novo Nordisk the Appeal Board ruled no breach of the Code.**

**The Panel ruled that the 'Incretins' backgrounder was misleading, exaggerated and not capable of substantiation with regard to its emphasis on weight reduction which had not been quantified. The SPC stated that weight reduction was between 1kg and 2.8kg and the data was less positive for 1.2mg Victoza in that mean body weight increased by 0.23kg in the 1.2mg Victoza and glimepiride group. On appeal by Novo Nordisk the Appeal Board upheld the Panel's ruling that the 'Incretins' backgrounder was not capable of substantiation.**

**The 'Victoza (liraglutide)' backgrounder quantified the weight loss data but did not include the weight gain data from the SPC. The Panel ruled that the backgrounder was misleading, not capable of substantiation and exaggerated as it did not reflect the totality or limitations of the data. On appeal by Novo Nordisk, the Appeal Board ruled no breach.**

**The Panel ruled breaches as the 'Incretins' and 'Victoza (liraglutide)' backgrounders were not presented in a balanced way and would raise unfounded hopes of successful treatment. The Panel ruled no breach in that these backgrounders were not promotional material as such and were not disguised promotion.**

**With regard to statements about BP the Panel noted that the backgrounders referred to reductions in systolic blood pressure (SBP). Section 5.1 of the SPC stated that Victoza decreased SBP by an average of 2.3 to 6.7mmHg from baseline and compared to active comparator the decrease was 1.9 to 4.5mmHg. The available data was for no longer than 26 weeks and related**

**only to certain combinations of liraglutide and oral antidiabetic (OAD) agents.**

**The 'Incretins' backgrounder stated that liraglutide's impact on, *inter alia*, reduction in SBP had been consistently demonstrated throughout the phase 3a LEAD (Liraglutide Effect and Action in Diabetes) trials. The reduction was not quantified and nor was any benefit claimed for the reduction. There was no claim implied or otherwise regarding protection against heart disease as alleged and thus no breach was ruled. A similar ruling was made regarding the 'Victoza (liraglutide)' backgrounder. The Panel ruled no breach of the Code in relation to allegations that the media articles claimed Victoza helped patients stay off insulin treatment and disparaged insulin treatment. These rulings applied to the backgrounders 'Incretins', 'Victoza (liraglutide)', 'Diabetes treatment' and 'Facts about type 2 Diabetes Treatment' and the press releases.**

**The Panel considered that the data regarding weight loss in both the lay and medical press releases were misleading, constituted a misleading comparison and were not capable of substantiation. Breaches were ruled. Upon appeal by Novo Nordisk of these two rulings the Appeal Board did not consider that the weight loss data in the press releases was incapable of substantiation or constituted a misleading comparison and ruled no breach in these regards. The press releases exaggerated the position and a breach was ruled. The Panel considered that a quotation in the press release that '… patients with type 2 diabetes can be confident they are controlling their blood sugar, and may benefit from weight loss. This is an important advance for patients with type 2 diabetes, many of whom are already overweight' implied that if patients on liraglutide lost weight the amount lost meant that they would no longer be overweight. This was not so. Breaches were ruled. One of these rulings was appealed by Novo Nordisk. The Appeal Board considered that the claim was capable of substantiation and no breach in that regard was ruled. The Panel considered that the quotation was misleading in referring to Victoza being an important advance with regard to the potential weight loss benefit and ruled a breach. The Panel, however, did not consider that the claim disparaged Byetta and thus ruled no breach in that regard.**

**The Panel did not consider that the references to the benefit of a reduction of SBP in either press release were unacceptable; no benefit for the reduction was claimed or implied. No breach was ruled.**

**The Panel ruled that the press releases were inconsistent with the SPC and were misleading with regard to the licensed indication. Upon appeal by Novo Nordisk, the Appeal Board ruled no breach.**

**The Panel considered that the inclusion of the very positive claims in the lay press release and the lack of information about side effects etc in effect turned the lay press release into an advertisement for a prescription only medicine and a breach was ruled. Upon appeal by Novo Nordisk, the Appeal Board ruled no breach.**

**The Panel considered that the press releases were not factual or balanced and would raise unfounded hopes of successful treatment particularly with regard to weight loss. Statements had been made in the lay press release to encourage the public to ask their health professional for Victoza. Each was ruled in breach.**

**Neither one of the opinion leaders quoted in one of the articles at issue nor a pharmacist quoted in another was a Novo Nordisk spokesperson. The Panel did not know if the pharmacist had been provided with a press pack. The Panel decided that on the information before it Novo Nordisk was not responsible under the Code for the comments attributed to either person and no breach was ruled.**

**In an interview, a health professional briefed by Novo Nordisk to give interviews in relation to the Victoza launch, stated that Victoza had undergone 'one of the most extensive programmes of development that we've seen in diabetes, probably well over ten years …'. In the Panel's view this implied that Victoza had undergone a more extensive development programme than other antidiabetic medicines. There was no information before the Panel to substantiate this implied comparison which was ruled in breach as it was misleading, not capable of substantiation and disparaged other medicines.**

**The Panel considered that other statements, that the risk of developing hypoglycaemia was extremely low, were misleading with respect to the safety of Victoza and breaches were ruled. The Panel further noted that in response to the question 'And how long has it been trialled for? There's a lot of concern sometimes about side-effects' the health professional did not refer to the side effect profile of Victoza, in particular he did not discuss the common or very common gastrointestinal effects of the medicine. The Panel ruled a breach as the answer to the question was misleading by omission.**

**The health professional stated that Victoza might stop type 2 diabetes progressing and stop the likelihood of patients needing to go onto insulin. There was no data before the Panel to show that this was so. Although β-cell function improved with Victoza it had not been demonstrated that patients would not need to progress onto insulin therapy. The Panel ruled breaches as the statement was misleading and exaggerated.**

**The Panel did not consider that it was inconsistent with the Authority's Constitution and**

**Procedure for Novo Nordisk to provide the health professionals used at the launch with details of Lilly's complaint which Lilly alleged was an attempt by Novo Nordisk to tarnish Lilly's reputation. The Panel had not been given details of what Novo Nordisk had provided to these health professionals. As a principle it was not necessarily unacceptable under the Code. The Panel considered that Lilly had not proven its allegation on the balance of probabilities. No breach was ruled including Clause 2.**

**Lilly had referred to the media activity in total and alleged breaches including Clause 2.**

**With regard to these general allegations and the press materials referred to above, the Panel considered that high standards had not been maintained and a breach was ruled. With regard to Clause 2, which was used as a sign of particular censure, the Panel considered that issuing misleading material to the press was a serious matter as was issuing a press release that advertised a prescription only medicine to the public. The Panel thus ruled a breach of Clause 2. Upon appeal by Novo Nordisk the Appeal Board, although concerned about the material, overturned this ruling.**

**With regard to the journal advertisements and other promotional material Lilly was concerned, *inter alia*, that the material was inconsistent with the Victoza SPC and implied that it could be used as a treatment for obesity and hypertension. Claims for weight loss, reductions in BP and changes in β-cell function could not be substantiated. The promotional material implied that Victoza delayed the progression of type 2 diabetes. The material was alleged to be misleading about side effects and the dosing of Victoza. Breaches of many clauses, including Clause 2, were alleged.**

**The Panel considered that the heading to a journal advertisement 'Do more than lower blood glucose' encouraged Victoza to be prescribed because of its effects beyond that of glycaemic control. In that regard the benefits of therapy had not been separated from or placed subsidiary to the main indication. A wider indication was implied. The reason to use Victoza, ie to reduce HbA1c, was the third piece of information on the page after the heading and the subheading which stated that 'Once-daily Victoza … impacts on multiple factors associated with type 2 diabetes …'. In boxed text equal emphasis was given to 'Reductions in HbA1c' as to reductions in weight, SBP and improvements in β-cell function.**

**The Panel considered that the secondary effects on weight, SBP and β-cell function had not been placed sufficiently within the context of the primary reason for prescribing Victoza (glycaemic control) or within the limit of the data. This was inconsistent with the SPC and a breach was ruled. Upon appeal by Novo Nordisk the Appeal Board overturned the ruling as it considered the advertisement was not inconsistent with the Victoza SPC.**

**The Panel did not consider that the advertisement invited a comparison with other antidiabetic medicines. It suggested that Victoza offered more than lowering of blood glucose but this was not necessarily unacceptable or disparaging. No breach was ruled.**

**The Panel considered the claim, 'Reductions in weight', too simplistic given the data. Although weight loss would benefit type 2 diabetics, the amount lost was small. Nonetheless some weight loss, however modest, was preferable compared with the weight gain associated with some other antidiabetic treatments. The SPC recorded weight gain data for Victoza 1.2mg plus glimepiride. It was important for health professionals to fully understand the magnitude of weight loss with Victoza and that not every patient would lose weight. This was not possible from the claim at issue. The Panel considered that the claim was misleading, ambiguous and exaggerated; it could not be substantiated for each Victoza dose (1.2mg or 1.8mg) or licensed combination. Breaches were ruled. Upon appeal by Novo Nordisk the Appeal Board overturned the Panel's rulings as it did not consider the claim was misleading or incapable of substantiation or exaggerated.**

**The BP changes had not been quantified in the advertisement. The claim 'Reductions in systolic blood pressure' implied that this applied to every licensed combination and was clinically and statistically significant. The SPC only referred to reductions in SBP vs active comparator and some of the results had not been statistically significantly different to placebo. It was important that health professionals fully understood the effects on BP. This was not possible from the claim at issue. The Panel ruled that the unqualified and unquantified claim was misleading, ambiguous and exaggerated and could not be substantiated. Breaches were ruled. Upon appeal by Novo Nordisk the Appeal Board overturned the Panel's rulings as it did not consider that the claim was misleading, ambiguous and exaggerated and it could be substantiated.**

**The Panel did not consider that the lollipop tree visual implied that Victoza could uproot type 2 diabetes and eliminate the illness. In the Panel's view it illustrated that there were a number of factors linked to type 2 diabetes. The Panel did not consider the visual was, in itself, inconsistent with the SPC as alleged and no breach was ruled.**

**The Panel considered that high standards had not been maintained; a breach was ruled which was overturned on appeal. The Panel did not consider the circumstances warranted a ruling of a breach of Clause 2.**

**The Panel considered that the claim 'SMC Pending' (Scottish Medicines Consortium) used on a reprint folder strongly implied that SMC approval was a formality or a matter of time rather than reflecting that Victoza at the time was going through the SMC process. The Panel ruled that the claim was ambiguous and thus misleading. The Panel considered that the SMC's active consideration of the product was sufficient with regard to the requirement to provide substantiation. The claim did not exaggerate the position nor was it a claim for a special merit. No breach was ruled. The Panel ruled no breach with regard to the allegation that Novo Nordisk had reproduced an official document without permission. The Panel did not consider that the use of the phrase 'SMC Pending' warranted a ruling of Clause 2.**

**The Panel did not consider that a claim in two leavepieces 'Victoza + metformin provide significant reductions in HbA1c compared with metformin alone …' was misleading given the published data. However, an explanation of statistical significance vs metformin in the leavepieces was ruled to be misleading in that every combination included metformin.**

**The Panel ruled breaches as it considered a chart in the leavepieces was misleading in that only the results for patients pretreated with OAD monotherapy were shown. The Panel considered that the data had been cherry-picked to show the results which demonstrated the largest positive difference for Victoza. Further breaches were ruled. The Panel considered that the positioning and presentation of a claim 'p<0.0001 versus metformin' reinforced the misleading impression of a statistically significant difference between the Victoza + metformin and the glimepiride + metformin data which was ruled to be misleading. The presentation of the data was inconsistent with the SPC and a breach was ruled. Upon appeal by Novo Nordisk, the Appeal Board overturned this ruling.**

**The Panel noted that a claim 'Statistically, fewer minor hypoglycaemic events were observed with Victoza in combination with metformin compared to metformin in combination with glimepiride (p<0.001)', reflected data from the LEAD 2 study and the SPC. In that regard the Panel did not consider that the claim was misleading. However, in the Panel's view, a claim 'In a separate study, no major hypoglycaemic events were observed with Victoza in combination with metformin and a thiazolidinedione' sought to minimize a clinician's concerns regarding the occurrence of hypoglycaemia in this treatment group. The SPC listed hypoglycaemia as common in patients being so treated. Omission of this data, given the inclusion of data about major hypoglycaemia, was ruled to be misleading.**

**Page 3 of the leavepieces presented the weight loss data for Victoza 1.2mg in combination with metformin although, as before, the heading and subheading did not make it clear that the results were for one dose of Victoza only. The Panel noted that the weight loss shown for Victoza plus metformin was within the range stated in the general comment in the SPC that sustained weight reduction over the duration of studies ranged between 1kg to 2.8kg (both 1.2mg and 1.8mg Victoza doses) and no breach was ruled. The Panel did not consider that the reference to early weight loss and the absence of p values in this regard implied a statistically significant difference as alleged and ruled no breach. The Panel ruled no breach with regard to absence of data for baseline body weight and the incidence of nausea, diarrhoea, vomiting, dyspepsia or visceral fat. The Panel did not consider the leavepiece was disparaging with regard to visceral fat data. Lilly had not made a detailed allegation in this regard. No breach was ruled.**

**The Panel considered that overall the leavepieces failed to maintain high standards and a breach was ruled. The Panel did not consider that the leavepieces warranted a ruling of a breach of Clause 2.**

**Pages 2 and 3 of two other leavepieces did not distinguish between the licensed indication and the benefits set out in the pharmacodynamics section of the Victoza SPC. On balance the Panel ruled that the data were presented in a misleading manner in that it appeared all the data was covered by the indication for Victoza and this was not so. A breach of the Code was ruled. The Panel did not consider that the data, in effect, promoted Victoza for unlicensed indications and thus no breach was ruled in that regard. The Panel did not consider that the leavepieces accurately reflected the balance of evidence as stated in the SPC with regard to major hypoglycaemic events and breaches were ruled. The Panel considered that although a complex table of data in the leavepieces would need to be read carefully to be understood, it was not misleading per se to omit the baseline data as alleged by Lilly. No breach was ruled. The Panel did not consider that the leavepieces were disparaging as alleged and no breach was ruled.**

**With regard to the claim in a leavepiece 'Dosing: use one device, once a day' the Panel considered that the front page of the leavepiece was not sufficiently clear that Victoza was to be used in combination with OADs rather than as monotherapy. The claim was misleading and the Panel's ruling of a breach of the Code was upheld on appeal by Novo Nordisk.**

**The Panel considered the claim 'Victoza allows convenient once-daily dosing at any time independent of meals' was ambiguous and misleading given the specific mention in the SPC that '… it is preferable that Victoza is injected around the same time of day, when the most convenient time of day has been chosen'. Upon**

**appeal by Novo Nordisk the Appeal Board overturned the Panel's ruling.**

**With regard to page 2, the Panel noted that it was stated that when Victoza was administered with metformin or with metformin plus a thiazolidinedione, no dose adjustments were needed. This was in line with the SPC and no breach was ruled.**

**The Panel ruled that high standards had not been maintained. The Panel was concerned that the leavepiece was not clear about the indications for a new product and implied that it could be used as monotherapy. The Panel decided on balance that the leavepiece brought discredit upon the industry and a breach of Clause 2 was ruled. Upon appeal by Novo Nordisk the Appeal Board overturned both of the Panel's rulings.**

**Lilly alleged that a patient booklet promoted Victoza to the public. It included the brand name no less than eighty-nine times and included promotional messages and minimised the risk of hypoglycaemia. Similar allegations were made about a patient website.**

**The Panel was concerned that the front page of the patient booklet included the product logo plus the claim 'New' which implied that the content was promotional. This impression was compounded by the positive statement 'Making a fresh start with Victoza'. Such promotional branding combined with a claim should not be used in patient materials. In the Panel's view the front page was, in effect, an advertisement for a prescription only medicine to the public and a breach was ruled. This ruling was upheld on appeal by Novo Nordisk.**

**The Panel did not consider that it was unacceptable to refer to NovoFine and NovoTwist needles in relation to the section 'Prepare your pen' and no breach was ruled.**

**The Panel considered that to state in the patient booklet that the risk of hypoglycaemia was minimised with Victoza was not fair or balanced; it misled with regard to the safety of the product and a breach was ruled.**

**Page 8 stated 'You should inject Victoza only once a day, at any time of day, with or without eating food first. But it's best if you use Victoza at the same time every day – so pick a time you won't forget'. The Panel did not consider that this page of the booklet promoted Victoza to the public as alleged. The information was in line with the SPC and no breach was ruled.**

**The Panel did not consider that the statement on page 18 'Here are a few tips to help you fit Victoza into your life better' was a promotional claim. This section referred to the need to take medicine regularly in order to get the full benefits and referred readers to sources of help. The Panel did not consider that the page advertised Victoza to the public. Readers would have been prescribed the product. The information was not unreasonable. The Panel ruled no breach.**

**The Panel noted its ruling of a breach in relation to the front page. However, the Panel did not consider that overall the booklet was promotional material that had been disguised as information to patients and ruled no breach.**
**The Panel ruled that the use of the Victoza logo and the claim 'new' meant that high standards had not been maintained. The Panel did not consider that on balance the circumstances warranted a ruling of a breach of Clause 2.**

**With regard to the patient website the Panel noted the comments it had made about the patient booklet at issue above. The Panel noted that many of the webpages now at issue included the brand logo. The Panel considered that this was unacceptable and constituted the promotion of a prescription only medicine to the public. A breach was ruled. The Panel considered that in this regard high standards had not been maintained and a breach was ruled. Upon appeal by Novo Nordisk the Appeal Board overturned the Panel's rulings as it did not consider the webpages constituted the promotion of a prescription only medicine to the public and that high standards had not been maintained. The Panel did not consider that overall the webpages were promotional material that had been disguised as information to patients. No breach was ruled. On balance the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2.**

**With regard to a formulary pack, Lilly made similar allegations to some of the allegations made about other promotional materials to health professionals.**

**The Panel considered that the purpose of Section 1 of the formulary pack overall was, *inter alia*, to establish a need for the additional benefits which might be provided by Victoza and to state where current therapies failed. The challenge of body mass index (BMI) and weight was given equal emphasis to glycaemic control. The Panel considered that the section implied that Victoza would positively address all of the unmet challenges. The Panel noted its comments and rulings above on Victoza's effect on secondary benefits. Breaches were ruled.**

**The Panel considered that the description of the unmet challenges in type 2 diabetes treatment in Section 1.6 'Unmet challenges' and Section 1.8 'Conclusion' could imply that no product currently available met any one of these challenges. The Panel considered that this was misleading as the challenges and the differences between current treatments were not defined in detail. The section disparaged current treatments and the impression given was not capable of substantiation. Breaches were ruled.**

**The Panel noted that Victoza was described as 'the first once-daily human glucagon-like peptide-1 (GLP-1) analogue developed for the treatment of T2D' in Section 1.7. The Panel noted, however, that although Victoza was the first once daily human GLP-1 analogue it was in fact the second GLP-1 analogue to be marketed. In that regard the Panel considered that the statement was ambiguous and thus misleading. It was unclear as to which part of the statement 'first' applied to. A breach was ruled which, on appeal by Novo Nordisk, was overturned by the Appeal Board.**

**The Panel ruled that high standards had not been maintained. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2.**

**The Panel considered that in Section 2.1 the bullet point 'Liraglutide is administered once daily, and can be given at any time of day, independently of meals …' was similar to a claim at issue above in that the detailed advice in the SPC that '… it is preferable that Victoza is injected around the same time of day, when the most convenient time of day has been chosen' was not included. The Panel therefore ruled a breach which, on appeal by Novo Nordisk, was overturned by the Appeal Board.**

**The Panel noted that in Section 2.1 the second bullet point referred to Victoza's indication and the sixth bullet point referred to improvements in glycaemic control; this was immediately followed by another bullet point 'Significant weight loss in comparison with comparator drugs when liraglutide was used in combination treatment'. Section 2.4 'Indication and dosing' clearly set out the approved indication. The Panel noted that Section 2.5 'The LEAD Programme' ended with the sentence 'The clinical benefits of treatment with liraglutide observed with LEAD trials are reported here'. A section 2.5.1 'Liraglutide and glycaemic control' was immediately followed by Section 2.5.2 'Liraglutide and body weight'. Section 2.5.3 'Liraglutide and SBP' referred to reductions in BP. The Panel considered that although the approved indication was given almost at the outset of Section 2 ie glycaemic control, additional benefits of therapy (effect on body weight and BP) were given equal emphasis. They were not unequivocally distinguished from the main goal of therapy. In that regard the Panel did not consider that the secondary benefits were adequately placed within the context of Victoza licensed indication. A breach was ruled. Upon appeal by Novo Nordisk the Appeal Board overturned this ruling.**

**The Panel did not consider that Section 2.3 implied that only Victoza improved β-cell function as alleged and no breach was ruled. The Panel was concerned, however, that the discussion about β-cell function did not explain the clinical significance of the findings. Although Victoza had been shown to improve β-cell function there was no data to show that this altered the clinical course of type 2 diabetes; some readers might assume that the data meant that Victoza delayed or halted its progression. In this regard the Panel considered that the information given was misleading and that its clinical importance had been exaggerated and breaches were ruled. The Panel did not consider that failure to specifically mention Byetta's effect on β-cell function in Section 2.3 of the formulary pack was in itself misleading and no breach was ruled.**
**Section 2.5, 'The LEAD Programme', stated that Buse *et al* (LEAD 6) was the first study to directly compare the two GLP-1 receptor agonists and that the study compared 1.8mg liraglutide added to metformin and/or glimepiride vs 10mcg exenatide. The Panel did not consider that Section 2.5 was misleading as alleged. The limited information about Buse *et al* (LEAD 6) did not claim differences between the products, it merely listed this study as contributing to the clinical data. No breach was ruled.**

**The Panel noted that Section 2.5.5.1' 'Hypoglycaemia', went into more detail than Section 2.5 in relation to outcomes from Buse *et al* (LEAD 6). The Panel considered that more information should have been included – particularly with regard to the doses of Victoza and Byetta used and the fact that the study was open label. Insufficient detail had been provided and thus the claim regarding differences in hypoglycaemia was misleading. Breaches were ruled. Upon appeal by Novo Nordisk the Appeal Board overturned these rulings.**

**Section 2.5.5.2 'Adverse events' included details of the data for nausea from the LEAD studies. The Panel did not consider the claim that nausea persisted longer with exenatide than liraglutide implied that no patient experienced nausea at 26 weeks. A preceding sentence described it as one of the most frequently reported adverse events. No breach was ruled.**

**The Panel did not consider that Section 2.6 would mislead readers to consider liraglutide as a licensed treatment for hypertension and obesity as alleged. No breach was ruled.**

**The Panel noted its rulings above and considered that high standards had not been maintained. A breach was ruled. Upon appeal by Novo Nordisk the Appeal Board overturned this ruling. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2.**

**The Panel noted that Section 3.1 included the claims that liraglutide was 'cost-effective compared with glimepiride when added to metformin monotherapy and with rosiglitazone when added to glimepiride monotherapy. The basis for these calculations was given in Tables 3.2 and 3.3. The clinical inputs 'Change in HbA1c', 'Change in SBP' and 'Change in BMI' were listed**

**in each table. Table 3.2 was based on a sub group of patients from Nauck *et al* (LEAD 2). The BMI data was not given in Nauck *et al* (LEAD 2). The Panel noted the comments it had made about Nauck *et al* (LEAD 2) when considering the journal advertisement.**

**The Panel considered that Tables 3.2 and 3.3 implied that the indications for Victoza included decreasing weight and SBP. This was not so. Section 3.1 of the formulary pack did not make the licensed indication clear nor the magnitude of the weight reduction and BP data. The material was incomplete thus misleading as alleged and breaches were ruled. Upon appeal by Novo Nordisk the Appeal Board overturned these rulings.**

**The Panel considered that, in the context of a health economic evaluation, Section 3.6 was not misleading with regard to the timing of administration of Victoza. The important consideration for an economic evaluation was the once-daily administration of Victoza and not that it had to be administered at about the same time each day. No breach was ruled.**

**Section 3.6 stated that the cost of self monitoring of blood glucose (SMBG) was added where necessary. It also stated that 'SMBG is not needed in order to adjust the dose of liraglutide. Therefore initiating liraglutide before a treatment that does require SMBG will have a favourable cost implication'. The Panel noted Lilly's view that the statement appeared to ignore the fact that when Victoza was started the majority of patients would already be on treatments that required SMBG. The section implied that liraglutide would be used prior to a sulphonylurea. The Panel considered that there might be a theoretical cost benefit but this was not made clear. A breach was ruled.**

**Section 3.8 'Number needed to treat one patient successfully to target' included results from a meta-analysis comparing patients treated to <7.0% HbA1c, <130mmHg SBP with no weight gain. The Panel noted that the composite endpoint had been made clear and was relevant to diabetic patients. The SPC included data for changes in weight and BP. The Panel considered that this section was not misleading with regard to the licensed indication as alleged. No breach was ruled.**

**The Panel noted its rulings above and considered that high standards had not been maintained. A breach was ruled. Upon appeal by Novo Nordisk the Appeal Board overturned this ruling. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2.**

**At the completion of its consideration of this case, the Appeal Board was concerned about the presentation of the complaint. The Appeal Board deplored the way the complaint had been constructed with so many repetitive allegations. The response to the complaint could also have been better constructed; however some of the problems were as a direct result of the nature of the complaint. The time taken by the Panel and the Appeal Board to consider this case could have been substantially reduced if the complaint had been better presented.**

Eli Lilly & Company Limited complained about Novo Nordisk Limited's launch activities for Victoza (liraglutide).

Victoza was licensed to treat type 2 diabetes mellitus to achieve glycaemic control firstly in combination with metformin or a sulphonylurea in patients with insufficient glycaemic control, despite maximal tolerated dose of monotherapy with metformin or sulphonylurea. Secondly, in combination with metformin and a sulphonylurea or a thiazolidinedione in patients with insufficient glycaemic control despite dual therapy.

Lilly's product Byetta (exenatide) was licensed for the treatment of type 2 diabetes mellitus in combination with metformin and/or sulphonylureas in patients who had not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.

Both products were glucagon-like peptide-1 (GLP) analogues. Victoza was administered once daily whereas Byetta was administered twice daily.

To improve gastrointestinal tolerability the starting dose of Victoza was 0.6mg daily to be increased to 1.2mg after at least one week. Some patients were expected to benefit from an increase in dose from 1.2mg to 1.8mg to further improve glycaemic control. Victoza could be administered once daily at any time however it was preferable to inject around the same time of the day.

Section 5.1 of the Victoza summary of product characteristics (SPC), pharmacodynamic properties, stated that Victoza stimulated insulin secretion in a glucose-dependent manner. Simultaneously, it lowered inappropriately high glucagon secretion, also in a glucose-dependent manner. Thus, when blood glucose was high, insulin secretion was stimulated and glucagon secretion was inhibited. Conversely, during hypoglycaemia liraglutide diminished insulin secretion and did not impair glucagon secretion. The mechanism of blood glucose lowering also involved a minor delay in gastric emptying. Liraglutide reduced body weight and body fat mass through mechanisms which involved reduced hunger and lowered energy intake.

Section 5.1 of the SPC also included additional information about the product in relation to, *inter alia*, glycaemic control, beta-cell function, body weight and blood pressure. With regard to body weight the SPC stated that Victoza in combination with metformin, metformin and glimepiride or metformin and rosiglitazone was associated with

sustained weight reduction over the duration of studies in a range from 1kg to 2.8kg. Larger weight reduction was observed with increasing body mass index (BMI) at baseline. The results from studies lasting 26 weeks were included in the SPC. The weight reduction data included in the SPC was as follows:

| Metformin add-on therapy | 1.8 mg liraglutide + metformin | 1.2 mg liraglutide + metformin | placebo + metformin | Glimepirde + metformin |
|---|---|---|---|---|
| N | 242 | 242 | 240 | 121 |
| **Mean body weight (kg)** | | | | |
| Baseline | 88.0 | 88.5 | 91.0 | 89.0 |
| Change from baseline | -2.79 | -2.58 | -1.51 | 0.95 |

| Glimepiride add-on therapy | 1.8 mg liraglutide + glimepiride | 1.2 mg liraglutide + glimepiride | Placebo + glimepiride | rosiglitazone + glimepiride |
|---|---|---|---|---|
| N | 231 | 234 | 228 | 114 |
| **Mean body weight (kg)** | | | | |
| Baseline | 83.0 | 80.0 | 81.9 | 80.6 |
| Change from baseline | -0.23 | 0.32 | -0.10 | 2.11 |

| Metformin + rosiglitazone add-on therapy | 1.8 mg liraglutide + metformin + rosiglitazone | 1.2 mg liraglutide + metformin + rosiglitazone | Placebo + metformin + rosiglitazone | N/A |
|---|---|---|---|---|
| N | 178 | 177 | 175 | |
| **Mean body weight (kg)** | | | | |
| Baseline | 94.9 | 95.3 | 98.5 | |
| Change from baseline | -2.02 | -1.02 | 0.60 | |

| Metformin + glimepiride add-on therapy | 1.8 mg liraglutide + metformin + glimepiride | N/A | Placebo + metformin + glimepiride | insulin glargine + metformin + glimepiride |
|---|---|---|---|---|
| N | 230 | | 114 | 232 |
| **Mean body weight (kg)** | | | | |
| Baseline | 85.8 | | 85.4 | 85.2 |
| Change from baseline | -1.81 | | -0.42 | 1.62 |

The SPC stated that over the duration of the studies Victoza decreased the systolic blood pressure on average by 2.3 to 6.7mmHg from baseline and compared to active comparator the decrease was 1.9 to 4.5mmHg.

The items at issue were considered as follows:

**A Public Relations Activity**

Lilly alleged that Novo Nordisk, through its agents and spokespersons, distributed inaccurate and misleading information about liraglutide to the UK consumer and medical press as evidenced by the articles and interviews which appeared in the Mail Online, Telegraph.co.uk, BBC Radio Ulster, ITV, the Pharmaceutical Journal, Clinical Pharmacist and the British Journal of Cardiology. Lilly believed that this coverage of liraglutide and its role in the management of type 2 diabetes was the result of inaccurate and misleading media and speaker briefing materials provided by Novo Nordisk. This assertion was based upon the consistency of the messaging supporting liraglutide as reported by the media and those that appeared in promotional materials. In inter-company dialogue Novo Nordisk acknowledged that before the launch of Victoza it had approached three of the health professionals referred to by Lilly to determine their willingness to provide their professional views and opinion on the product. Thus, contrary to Novo Nordisk's suggestion, the involvement of these health professionals was clearly not entirely independent. The company would have known their opinions about liraglutide; this was material to the fact that all of the health professionals mentioned by Novo Nordisk were then involved in public relations activities, supporting the launch of Victoza. Lilly asserted that the co-ordination and briefing was undertaken either by Novo Nordisk and/or its third party agent. Indeed, if Novo Nordisk and/or its agent(s) did not brief its spokespersons, as was suggested in inter-company dialogue, then this was clearly inconsistent with the Code.

From the coverage of liraglutide in the consumer and medical press Lilly believed it was likely that the media and speaker briefings had been held to advertise and promote the availability of liraglutide, a prescription only medicine, to the general public and to health professionals. Based on the articles, Lilly alleged that the information provided by Novo Nordisk was not entirely factual, misleading, employed sensationalist and promotional language and was not balanced or appropriately measured. Lilly was particularly concerned that the coverage in the consumer press was misleading regarding the precise licensed indication of liraglutide and its safety. The coverage raised unfounded hopes of successful treatment with respect to the unbalanced and often unqualified discussion of weight loss and blood pressure reductions associated with liraglutide which encouraged members of the public to ask doctors to prescribe liraglutide. Further, audiences were misled about the product's licensed indication and in this regard the activities and materials which supported the launch of liraglutide did not encourage its rational use.

Novo Nordisk stated that in inter-company correspondence Lilly named six independent health professionals and alleged that through these agents Novo Nordisk provided misleading and inaccurate information to the press. As Novo Nordisk highlighted to Lilly, only three of the named health professionals were contacted by Novo Nordisk before the launch of liraglutide in order to determine their willingness to provide their own

independent professional views on the compound to potentially interested lay and medical press journalists. As seen from the briefing materials, together with the practical information provided in advance of the interviews a script was not included as to what should be included in the interviews. The information communicated by these journalists was their own professional independent opinion based on their extensive clinical and practical experience with diabetes and the product gained from their participation in clinical trials during the development of liraglutide.

The three other named health professionals were not approached by Novo Nordisk and were not asked to participate in any launch activities for liraglutide.

Novo Nordisk submitted that therefore, Lilly's allegation that 'the remarkable consistency of the messaging supporting liraglutide' was based on inaccurate and misleading media and speaker briefing by Novo Nordisk was unfounded.

Novo Nordisk provided copies of the Media Backgrounder Package which consisted of seven separate documents 'Changing Diabetes' (ref UK/LR/0509/0143), 'Diabetes Facts' (ref UK/LR/0509/0144), 'Diabetes Information' (ref UK/LR/0509/0145), 'Incretins' (ref UK/LR/0509/0146), 'Facts about type 2 Diabetes Treatment' (ref UK/LR/0509/0147), 'Novo Nordisk - the Diabetes Care Company' (ref UK/LR/0509/0148) and 'Victoza (liraglutide)' (ref UK/LR/0509/0149). These were to be distributed within the press pack. The speaker briefing pack for the Victoza media launch included details of the launch schedule for Novo Nordisk's three speakers. One of the speakers gave a presentation 'Changing Times, Changing Diabetes'. Another speaker presented on the patient perspective and was to give interviews including on 8 July on 'This morning' and be available for more interviews. Speakers were available to answer questions either in front of the whole audience or on an individual basis. The brief for a third speaker referred to radio interviews to be held on 7 July 2009.

Novo Nordisk had issued two press releases, one for the medical press and one for the lay press. Both press releases included a section headed 'Additional benefits' these being weight loss, reduction in systolic blood pressure and improved beta-cell function.

**1 Article in the Mail Online 'The once-a-day diabetes jab that fights obesity'**

**COMPLAINT**

Lilly alleged that the title and content of the article clearly invited the lay reader to consider that liraglutide was primarily an anti-obesity treatment in patients who happened to have type 2 diabetes. Readers were not told that the main measure of liraglutide's effectiveness was the establishment of adequate blood sugar control as measured by reductions in glycosylated haemoglobin (HbA1c) after six months or one year. Whilst a balanced and appropriately focused discussion of obesity as a risk factor associated with type 2 diabetes was reasonable, this article focussed almost entirely on the 'obesity time-bomb' which underlay the implicit message that this could be averted by treatment with liraglutide. The reader was led to believe that managing obesity with liraglutide was the primary therapeutic goal and by preventing this, type 2 diabetes and its complications could be avoided or improved. The licensed indication of liraglutide, to achieve glycaemic control in combination with other antidiabetic agents, was relegated almost to an anecdote in the body of the article where again, by its direct association with the numerous claims promoting the weight reducing benefits of liraglutide, this critical information was effectively buried thus ensuring that the precise indication of liraglutide remained ambiguous. Given the absence of the qualification that liraglutide should be used in combination with other antidiabetic agents, it was implied that liraglutide could be used as monotherapy. This misleading impression was further enhanced by the repeated and unqualified emphasis on the once-daily dosing which suggested to the lay reader that all that type 2 diabetics needed to manage their condition was a treatment regimen that only involved once-daily dosing with liraglutide.

The discussion of the weight reduction benefit associated with liraglutide was often couched by an off-licence statement such as 'A new diabetes jab could help fight obesity caused by insulin intake' and 'Experts say that the injection, called Victoza, could help prevent thousands of type 2 diabetes suffers having to take insulin – which can cause weight gain'. These statements were misleading and disparaged insulin. To single out insulin in this regard was unbalanced given that sulphonylureas were also associated with weight gain. The alarmist language adopted to discuss the risk of obesity and weight gain associated with insulin was of concern given that many readers would be insulin-dependent type 2 diabetics for whom liraglutide was not an option. Further, the assertion that liraglutide could help type 2 diabetics from becoming insulin-dependent or '… help sufferers to stay off insulin' was misleading, unsubstantiated and raised unfounded hopes and expectations of successful treatment with liraglutide in breach of Clauses 7.2, 7.3, 7.4 and 8.1 of the Code.

Similarly, statements such as 'Another benefit is that it lowers blood pressure, which is a factor in heart disease' and quotations attributed to a Novo Nordisk spokeswomen, such as '… this treatment has a positive effect on blood pressure levels' were intended to lead the lay reader to infer that liraglutide was also licensed to treat '… high blood pressure levels' and, by association, complications such as heart disease. The latter information was an unqualified generalisation, misleading and could not be substantiated. It should, more accurately, refer to systolic blood pressure, clarify and qualify

the statistical and clinical significance of any blood pressure reduction with respect to particular dosages of liraglutide. Notwithstanding the omission of the latter, Lilly questioned the relevance of this information to a lay audience. The prominence that this was given was clearly aimed at promoting the additional unlicensed benefits of liraglutide to the public. The reference to and emphasis on these other attributes of liraglutide, other than its effect on glycaemic control, was inconsistent with the liraglutide SPC and therefore in breach of Clause 3.2.

The overwhelming emphasis on the weight reduction benefit of liraglutide was likely to raise unfounded hopes of successful treatment with regard to the sustained and long-term reduction in weight loss associated with liraglutide; no data was currently available to substantiate any such suggestion. The same could be said of the implied claim that liraglutide offered protection against heart disease by virtue of its unqualified effect on blood pressure; this was a breach of Clauses 7.2, 7.3, 7.4 and 7.10.

The promotional nature of the article was evidenced by four separate mentions of Victoza, which went beyond the purpose of identification; numerous statements such as 'Victory for Victoza?' and 'Scientists have developed a revolutionary once-a-day injection that controls the symptoms of diabetes and helps fights obesity' read like advertising copy. This was a breach of Clauses 12.1, 22.1, 22.2 and 22.5. The advertising of liraglutide to the public was further emphasised by similarly sensationalist quotations attributed to a Novo Nordisk spokesman such as 'It could herald a new age in diabetes treatment'. The latter clearly exaggerated the facts given that liraglutide was the second GLP-1 analogue to be marketed. The quotation attributed to another Novo Nordisk spokesman that 'This is an important advance for patients with type 2 diabetes, many of who are already overweight' again invited consideration of the weight reduction benefit of liraglutide but critically, also implied that products such as metformin and the first GLP-1 analogue, Byetta, offered no such benefit or advance in this regard. Similarly, statements that '…[liraglutide] also reduces weight - which is extraordinarily good news' again implied that products such as Byetta offered no additional weight loss benefit and were consequently entirely ordinary; this was not the case given that metformin was the initial treatment of choice for many overweight, newly diagnosed type 2 diabetics. A breach of Clauses 7.2 and 8.1 was alleged.

The misleading and promotional nature of the Novo Nordisk briefing materials was evidenced by the statement that '… the jab will soon be available free on the NHS'. This suggested that prescribing information was included in the briefing materials, contrary to the Code and implied that other antidiabetic treatments were not available free on the NHS.

Given the intended audience, none of the Novo Nordisk spokespersons referred to the safety and tolerability of liraglutide particularly with regard to the incidence of gastrointestinal side effects, which occurred very commonly, and hypoglycaemia which occurred commonly or very commonly when it was used in combination with glimepiride, metformin and glimepiride or metformin and rosiglitazone. This was an important omission when considered alongside the copious discussion promoting the benefits of liraglutide; one which was likely to mislead the reader about the potential risks associated with it. This was a breach of Clauses 7.2, 7.9 and 7.10.

**RESPONSE**

Novo Nordisk refuted the allegation that the quotations in the Daily Mail article were based on Novo Nordisk speaker briefings. Two of the three health professionals referred to in the article had never been contacted by Novo Nordisk in relation to liraglutide, and thus the quotations reflected their own independent professional opinions. Although the third quotation was by a physician who Novo Nordisk had asked to provide his own professional and independent opinion about liraglutide, his statement was fully aligned with the Victoza SPC which stated that 'Liraglutide reduces body weight and body fat mass through mechanisms involving reduced hunger and lowered energy intake'. Further he did not suggest that a primary indication of Victoza was weight reduction ('With Victoza, patients with type 2 diabetes can be confident they are controlling their blood sugar and **may** benefit from weight loss. This is an important advance for patients with type 2 diabetes, many of whom are already overweight' (emphasis added)).

The media backgrounder press packs provided by Novo Nordisk contained information about diabetes, the company and liraglutide. The material clearly stated that liraglutide was indicated for the treatment of type 2 diabetes in combination with metformin or sulphonylurea and in combination with metformin plus sulphonylurea or metformin plus thiazolidinedione. The potential weight sparing and blood pressure lowering features of liraglutide were highlighted, in accordance with the SPC as additional and relevant benefits of the medicine. As such, the press packs provided a comprehensive and accurate clinical perspective, in line with the SPC. The briefing material did not suggest that liraglutide was licensed to treat obesity and hypertension, and if, as alleged by Lilly this impression had been given by the journalists, this was not in response to information provided by Novo Nordisk.

Further, Novo Nordisk did not have any editorial control as to the content of the interviews and articles, and did not believe it could be held responsible for the way in which the journalists chose (in their absolute discretion) to report Victoza, nor could it be held responsible for the fact that the article did not mention Byetta and its weight

reducing benefits and the fact that Victoza must be used in combination with specific oral antidiabetic medicines, and nor did Novo Nordisk believe that the likely interpretation and assumption taken from this article was that liraglutide was the only treatment for type 2 diabetes which could provide long-term weight loss and cardiovascular protection, given the omission of the mention of other agents, such as Byetta.

The emphasis made by the journalist that insulin treatment was associated with weight gain in the majority of patients, and treatment with liraglutide could lead to weight loss was widely accepted by health professionals.

Novo Nordisk denied any breach of the Code.

**PANEL RULING**

The Panel noted that complaints about articles in the press were judged on the information provided by the pharmaceutical company or its agent to the journalist and not on the content of the article itself. Clause 22.1 prohibited the advertising of prescription only medicines to the general public. Clause 22.2 permitted information about prescription only medicines to be supplied directly or indirectly to the general public but such information had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific prescription only medicine. Lilly had not seen Novo Nordisk's materials. Its complaint was based on press articles.

The Panel noted that Novo Nordisk had not specifically confirmed whether the journalist from the Daily Mail had attended the press launch or whether an additional interview was arranged for him as part of the media activity referred to in the speakers' briefing. The article at issue quoted three health professionals. One of whom was reported as stating 'With Victoza patients with Type 2 diabetes can be confident they are controlling their blood sugar and may benefit from weight loss'. The Panel noted that this quotation was included in the medical and lay press releases issued by Novo Nordisk.

The Panel considered the question of Novo Nordisk's responsibility under the Code for comments made by health professionals. It was clear that Novo Nordisk was responsible for the quotations included in its press pack. The Panel noted that Novo Nordisk had involved three health professionals with the launch who were briefed by Novo Nordisk which had facilitated their availability for interviews. The Panel decided that Novo Nordisk was responsible under the Code for comments made by the three health professionals. Companies could not use independent experts as a means of avoiding the restrictions in the Code.

Novo Nordisk was not responsible for the content of the article in the Daily Mail per se. The Panel would consider Lilly's allegations in relation to Novo Nordisk's press materials which had not been seen by Lilly. The Panel considered that each individual piece had to be capable of standing alone with regard to the requirements of the Code. An otherwise misleading statement in one backgrounder or press release could not be qualified by statements in other material. The Panel examined the Media Backgrounder Package and the two press releases.

The Media Backgrounder Package consisted of seven documents 'Changing Diabetes', 'Diabetes Facts', 'Diabetes Information', 'Incretins', 'Facts about type 2 Diabetes Treatment', 'Novo Nordisk – the Diabetes Care Company' and 'Victoza (liraglutide)'.

The backgrounder 'Facts about type 2 Diabetes Treatment' included a number of sections, firstly 'Lowering blood glucose' which was followed by a section 'Beyond blood glucose' which gave information about obesity, high blood pressure and elevated cholesterol.

The backgrounder 'Incretins' mentioned GLP-1 and Victoza. It was not clearly stated that Victoza was indicated in combination with metformin and/or a sulphonylurea or metformin and a thiazolidinedione. Victoza was not indicated for first line use or as monotherapy. In a section headed 'Victoza (liraglutide)' this backgrounder referred to liraglutide lowering glucose levels by stimulating insulin release when glucose levels became too high. It also stated that liraglutide's impact on HbA1c control, weight loss, reduction in systolic blood pressure and improved beta-cell function had been consistently demonstrated throughout the phase 3a Liraglutide Effect and Action in Diabetes (LEAD) trials. The document referred to the European Medicines Evaluation Agency's (EMEA's) positive opinion 'recommending a marketing authorisation for the treatment of type 2 diabetes'.

Immediately below the heading of the 'Victoza (liraglutide)' backgrounder the indication for the product was stated followed by a section 'The importance of type 2 diabetes risk factors' which stated that addressing risk factors for cardiovascular disease, including HbA1c, body weight and blood pressure was key to managing type 2 diabetes. It included similar statements regarding Victoza's mechanism of action to those in the 'Incretin' backgrounder. Quantative data was provided about the results of clinical studies (LEAD 1, LEAD 2 and LEAD 4) with regard to HbA1c reduction, weight loss, hypoglycaemia incidence, systolic blood pressure and cholesterol levels. A further open label study comparing liraglutide with exenatide was mentioned (LEAD 6). Detailed data was included.

The medical press release and lay press releases bore the same reference number. Both featured boxed text on the first page which stated the

indications for Victoza.

Both press releases stated under a section headed 'Additional benefits' that Victoza could help patients achieve weight loss by increased satiety and delayed gastric emptying, and thus reduced calorie intake. This was referred to as an important factor in treating type 2 diabetics as many were overweight. This section also referred to reduced systolic blood pressure and improved beta-cell function. The quotation 'With Victoza, patients with type 2 diabetes can be confident they are controlling their blood sugar, and may benefit from weight loss. This is an important advance for patients with type 2 diabetes, many of whom are already overweight' was also included. A similar section appeared in the lay press release. The medical press release included a section on comparative studies.

The lay press release included statements 'Victoza is the first once-daily human Glucagon-like peptide-1 (GLP-1) analogue', 'Victoza lowers blood sugar levels by stimulating the release of insulin only when glucose levels become too high' and 'Victoza is a convenient once-daily injection that can be taken any time of day, irrespective of meals' which appeared immediately beneath the heading 'Novo Nordisk launches Victoza (liraglutide) in the UK, a new once-daily treatment for type 2 diabetes'.

The Panel noted that none of the press pack (the press releases and relevant backgrounders) included details of precautions for use or side effects of Victoza. This was likely to mislead regarding the overall benefits of the product as alleged. Breaches of Clauses 7.2, 7.9 and 7.10 were ruled with regard to the materials for the press.

The Panel was concerned that the overall impression of the press pack was that Victoza was to be prescribed to control blood glucose, reduce weight, reduce blood pressure and improve beta-cell function. The materials were not clear regarding the licensed indication as set out in Section 4.1 of the SPC. The materials placed equal emphasis on the information set out in Section 5.1 of the SPC with regard to reductions in weight and blood pressure and improved beta-cell function. Readers might be confused as to the precise indication for Victoza. Little mention was made that the product was only to be prescribed as combination therapy when first and/or second line oral treatment options had failed to produce adequate glycaemic control.

The Panel noted that according to the SPC weight loss from baseline ranged from 2.79kg to 0.23kg for patients taking 1.8mg liraglutide in combination with metformin or glimepiride respectively. For patients on 1.2mg liraglutide plus metformin weight loss was 2.58kg whilst those who were treated with 1.2mg liraglutide plus glimepiride gained 0.32kg. The change in baseline for patients not taking liraglutide ranged from -1.51kg to +2.11kg.

The Panel questioned whether the emphasis on weight reduction in the press pack was supported by the data. Marre *et al* (2009) (LEAD 1) compared the effects of combining liraglutide or rosiglitazone or placebo with glimepiride. Mean reductions in weight from baseline were 0.2kg with liraglutide 1.8mg and 0.1kg with placebo. Increases occurred with liraglutide 1.2mg (0.3kg) or rosiglitazone (2.1kg). Unlike rosiglitazone weight did not increase substantially with liraglutide and the differences between rosiglitazone and liraglutide were statistically significant (-2.3 to -1.4kg $p<0.0001$) although there were no significant differences compared to placebo.

The study authors listed the short duration (26 weeks) as a limitation of the trial. Zinman *et al* (July 2009) (LEAD 4) showed statistically significant greater weight loss in the liraglutide groups compared with the placebo group ($p<0.0001$) (added to a regimen of metformin and rosiglitazone). The weight loss in the 1.8mg liraglutide group (2 ± 0.3kg) was statistically significantly different to the weight loss in the 1.2mg liraglutide group (1 ± 0.3kg) ($p=0.011$).

Buse *et al* (2009) (LEAD 6) compared the addition of liraglutide 1.8mg once daily or exenatide 10mcg twice daily to patients inadequately controlled on maximally tolerated doses of metformin, sulphonylurea or both. Differences between the products were noted. However, the mean weight reduction for liraglutide (3.24kg) and for exenatide (2.87kg) were similar and similar proportions of patients lost weight, 78% with liraglutide compared to 76% with exenatide.

The Panel noted that the data was based on mean body weight for a group of patients but this was not made clear in the press pack. The impression was given that every patient taking liraglutide would lose weight and this was not so. Buse *et al* (LEAD 6) showed that 22% of patients lost no weight. No information was given about this group of patients; some might have gained weight.

The Panel considered that the statement in the backgrounders 'Incretins' and 'Victoza (liraglutide)' which referred equally to Victoza's impact on HbA1c control, weight loss, reduction in systolic blood pressure and improved beta-cell function being consistently demonstrated in clinical trials were misleading with regard to the licensed indication for Victoza and inconsistent with the SPC. It appeared that Victoza could be prescribed as much for its additional benefits as its licensed indication ie glycaemic control. A breach of Clause 3.2 was ruled. This ruling was appealed.

The Panel noted that Novo Nordisk in its response had referred to the potential 'weight sparing' feature of liraglutide. This phrase was not used in the press materials. The Panel considered that the emphasis in the backgrounder documents on weight reduction was misleading. The available data was for no longer than 26 weeks and related only to certain combinations of liraglutide and oral antidiabetic agents. The weight reduction had not

been quantified in the 'Incretins' backgrounder and in the Panel's view this was very important. The SPC clearly stated that the reduction ranged between 1kg and 2.8kg. Given the association between type 2 diabetes and excess body weight it was important that the magnitude of potential weight loss was made clear. Even with the weight loss reported with Victoza, most patients in the LEAD studies were likely to remain overweight if not obese (BMI>30). The data was less positive for the 1.2mg Victoza dose in that mean bodyweight increased by 0.23kg in the 1.2mg liraglutide and glimepiride group. The Panel considered that the 'Incretins' backgrounder was misleading in this regard and not capable of substantiation. Breaches of Clauses 7.2 (not appealed) and 7.4 (this ruling was appealed) were ruled. It was also exaggerated and a breach of Clause 7.10 was ruled. There was no comparison in the 'Incretins' backgrounder and thus no breach of Clause 7.3 was ruled.

With regard to the backgrounder 'Victoza' (liraglutide) the Panel noted that some of the weight change data (increases and reduction) had been quantified. However the impression was given that all patients on a Victoza combination would lose weight and that was not so. The SPC data showing weight gain for liraglutide 1.2mg was not included. The Panel considered that although detailed data was presented this was not comprehensive. The backgrounder 'Victoza (liraglutide)' was misleading as it did not reflect the totality or limitations of the data and was not capable of substantiation. Breaches of Clauses 7.2, 7.3 and 7.4 were ruled. The backgrounder was exaggerated and a breach of Clause 7.10 was ruled. These rulings were appealed.

The Panel noted its ruling of a breach of Clauses 7.2, 7.9 and 7.10 in relation to a general allegation regarding the absence of information about precautions for use or side effects. The Panel was concerned that neither of the backgrounders 'Incretins' and 'Victoza (liraglutide)' referred to side effects and contraindications for the product. Neither was it sufficiently clear that the product was to be used second or third line and in combination with oral antidiabetics. The Panel considered that the backgrounders were not presented in a balanced way and would raise unfounded hopes of successful treatment. A breach of Clauses 7.2 and 22.2 was ruled. The Panel did not consider the backgrounders were promotional material as such. They were not disguised promotion and no breach of Clauses 12.1 and 22.1 was ruled.

With regard to statements about blood pressure the Panel noted that the backgrounders referred to reductions in systolic blood pressure. Section 5.1 of the SPC stated that Victoza decreased systolic blood pressure by an average of 2.3 to 6.7mmHg from baseline and compared to active comparator the decrease was 1.9 to 4.5mmHg. The available data was for no longer than 26 weeks and related only to certain combinations of liraglutide and oral antidiabetic agents. Marre *et al* (LEAD 1) stated that the decreases in systolic blood pressure with Victoza 1.2 mg or 1.8mg combined with glimepiride (2.6 – 2.8Hg) were not statistically significantly different from placebo or rosiglitazone combined with glimepiride (0.9 – 2.3mmHg).

Nauck *et al* (2009) (LEAD 2) stated that the treatment differences compared with glimepiride plus metformin were statistically significant (1.2mg Victoza plus metformin reduction of 3.2mmHg, p=0.0128 and 1.8mg Victoza plus metformin reduction of 2.7mmHg, p=0.0467).

Zinman *et al* (LEAD 4) stated that the 1.2 and 1.8mg liraglutide groups (in combination with metformin plus rosiglitazone) had statistically significant reductions in mean systolic blood pressure compared with the placebo group (placebo corrected difference 1.2mg Victoza combination reduction of 5.6mmHg p<0.0001 and 1.8mg Victoza combination reduction of 4.5mmHg p=0.0009).

Russell-Jones *et al* (2009) (LEAD 5) stated that the difference between 1.8mg Victoza in combination with metformin plus glimepiride, reduction of 4mmHg and placebo was not statistically significant.

Buse *et al* (LEAD 6) stated that systolic blood pressure for 1.8mg liraglutide (plus metformin or sulphonylurea or both) was reduced by 2.51mmHg.

The 'Incretins' backgrounder stated that liraglutide's impact on, *inter alia*, reduction in systolic blood pressure had been consistently demonstrated throughout the phase 3a LEAD trials. The reduction was not quantified and nor was any benefit claimed for the reduction. There was no claim implied or otherwise regarding protection against heart disease as alleged and thus no breach of Clauses 7.2, 7.3, 7.4 and 7.10 was ruled.

The 'Victoza liraglutide' backgrounder stated that addressing risk factors for cardiovascular disease was one of a number of risk factors key to managing diabetes. Liraglutide's impact on, *inter alia*, reduction in systolic blood pressure had been consistently demonstrated throughout the phase 3a LEAD trials. The data from Marre *et al* (LEAD 1), Nauck *et al* (LEAD 2) and Buse *et al* (LEAD 6) were not quantified. The data from Zinman *et al* (LEAD 4) was quantified but did not give the placebo corrected differences. The Panel did not consider that the backgrounder implied a claim for protection against heart disease as alleged and thus no breach of Clauses 7.2, 7.3, 7.4 and 7.10 was ruled.

The Panel did not consider that the backgrounders 'Incretins' and 'Victoza (liraglutide)' disparaged insulin treatment. Insulin was only mentioned in relation to the effect of naturally occurring insulin rather than treatment with it. There was no mention of Victoza helping patients stay off insulin. The Panel ruled no breach of Clauses 7.2, 7.3, 7.4 and 8.1.

The backgrounder 'Diabetes treatment' referred to

insulin becoming the preferred option when tablets were not enough to manage type 2 diabetes. A similar statement appeared in the backgrounder 'Facts about type 2 Diabetes Treatment'. The Panel did not consider that these two backgrounders disparaged insulin treatment as alleged. There was no statement to the effect that Victoza helped patients stay off insulin. The Panel ruled no breach of Clauses 7.2, 7.3, 7.4 and 8.1.
Turning to the speaker briefing pack the Panel did not consider that the contents were unacceptable as alleged. The material was primarily about the logistics for the launch event and other activities. The launch was described as being key to raising awareness about Victoza; it would increase understanding of the product and the benefits to patients and physicians. The Panel considered it was surprising that no information about Victoza was provided to the speakers. Nor was any information or guidance given about compliance with the Code. The Panel considered that Lilly's allegations about the speaker briefing pack were addressed by the Panel's rulings about the other press materials. It thus decided not to make any rulings about the speaker briefing pack.

With regard to the press releases the Panel was concerned that they were wholly positive about the product. None of the side effects or contraindications had been included. The use of Victoza in combination with oral antidiabetic medicines and that it would be used in effect second or third line when oral antidiabetic therapy was not tolerated or glycaemic control was insufficient despite dual therapy was not made clear. With regard to possible weight loss the press releases did not quantify the amount and the Panel considered that this was very important. Clinicians and patients might be misled by the very positive but undetailed weight reduction claims. The Panel considered that the data regarding weight loss in both the lay press release and the medical press release were misleading and not capable of substantiation. Breaches of Clauses 7.2 (not appealed) and 7.3 and 7.4 (both appealed) were ruled. The press releases exaggerated the position and a breach of Clause 7.10 was ruled. The Panel considered that the health professional's claim that '… patients with type 2 diabetes can be confident they are controlling their blood sugar, and may benefit from weight loss. This is an important advance for patients with type 2 diabetes, many of whom are already overweight' implied that if patients on liraglutide lost weight the amount lost meant that they would no longer be overweight. This was not so. Breaches of Clauses 7.2, 7.3 and 7.10 were ruled. A ruling of a breach of Clause 7.4 was appealed. The Panel considered that the quotation was misleading in referring to Victoza being an important advance with regard to the potential weight loss benefit. The data for Byetta, Buse *et al*, LEAD 6, demonstrated a similar weight loss for both products and both were licensed for glycaemic control. A breach of Clause 7.2 was ruled. The Panel, however, did not consider that the claim disparaged Byetta and thus no breach of Clause 8.1 was ruled.

The Panel did not consider that the references to the benefit of a reduction of systolic blood pressure in either press release were unacceptable; no benefit for the reduction was claimed or implied. No breach of Clauses 7.2, 7.2, 7.4 and 7.10 was ruled.

The Panel considered that the press releases were inconsistent with the SPC and were misleading with regard to the licensed indication. Breaches of Clauses 3.2 and 7.2 were ruled. These rulings were appealed.

The Panel considered that the inclusion of the very positive claims in the lay press release and the lack of information about side effects etc in effect turned the lay press release into an advertisement for a prescription only medicine and a breach of Clause 22.1 was ruled which was appealed.

The Panel considered that neither press release presented the information in a factual balanced way. The press releases would raise unfounded hopes of successful treatment particularly with regard to weight loss. Statements had been made in the lay press release to encourage the public to ask their health professional for Victoza. Each was ruled in breach of Clause 22.2.

The material was not clear that patients with type 2 diabetes using insulin could not be given Victoza. However, the Panel did not consider that the press releases disparaged insulin treatment. Insulin was only mentioned in relation to the effect of naturally occurring insulin rather than treatment with it. There was no mention of Victoza helping patients stay off insulin. The Panel ruled no breach of Clauses 7.2, 7.3, 7.4 and 8.1.

The Panel ruled no breach of Clause 22.5 which required that companies were responsible for information about products issued by their public relations agency. This was a statement of principle and not a requirement that could be breached.

**APPEAL BY NOVO NORDISK**

Novo Nordisk emphasized its general concern about the significant discrepancies between the Panel's rulings and the MHRA pre-vetting approvals and noted that the following Victoza launch materials, ruled in breach of the Code by the Panel, had been pre-vetted by the MHRA:

1 all the media backgrounders referred to;
2 the press releases;
3 the journal advertisement;
4 the reprint folders;
5 the leavepieces; and
6 the website.

The patient support booklet and the Formulary Pack were not pre-vetted by the MHRA, as they were issued after receipt of the letter of 29 June 2009 in which the MHRA stated that it no longer needed to pre-vet Novo Nordisk's promotional materials. The normal period for pre-vetting was up to six months

and the Blue Guide stated that 'this time period may be reduced or extended depending on the quality of the initial advertising material submitted and other relevant factors'. Novo Nordisk noted that the MHRA's pre-vetting of Victoza continued for just one month.

Novo Nordisk noted that the Memorandum of Understanding between the ABPI and MHRA of November 2005 confirmed the importance of co-operation between the MHRA and PMCPA 'to promote efficient complaint procedures without compromising the independence of each party'. The company further appreciated that 'The ABPI Code covers and extends beyond the UK law and it is thus possible that material pre-vetted and approved by the MHRA might subsequently be ruled to be in breach of the ABPI Code' and that 'Material subject to the ABPI Code considered by the MHRA as being potentially in breach of UK regulations, is very likely also to be in breach of the ABPI Code'.

However, Novo Nordisk submitted that the converse was likely to be true in that materials approved against statutory provisions (ie the Medicines Act 1968, the Medicines (Advertising) Regulations 1994/3144 ('Advertising Regulations') and the other delegated legislation made under the Act, and the MHRA Blue Guide) under the MHRA pre-vetting procedure should not subsequently be held to be in breach of equivalent provisions of the Code. Whilst the respective roles of the two bodies as envisaged in the Memorandum of Understanding might differ, it seemed wholly inappropriate for the decision of the MHRA fulfilling its statutory role to be later 'overruled' by the PMCPA.

Specifically Novo Nordisk submitted that: Clause 3.2 of the Code was directly reflected by Regulation 3A (1) of the Advertising Regulations; and Clauses 7.2, the requirement in Clause 7.3 that promotion must not be misleading and Clause 7.4 of the Code were to a material extent matched by the provisions of Regulation 3A (2) and (3) of the Advertising Regulations and Paragraph 4.3 of the Blue Guide. Clause 22.1 of the Code mirrored Paragraph 5.2 of the Blue Guide which related to Regulation 7 of the Advertising Regulations.

Novo Nordisk submitted that as the effect and intent of these respective provisions were effectively identical the apparent inconsistency in interpretation as between the MHRA and PMCPA was therefore difficult to understand. Novo Nordisk further submitted that with respect to all of the alleged breaches below in relation to materials previously pre-vetted by the MHRA, those based on Clauses 3.2 and 22.1 (and to a substantial degree Clauses 7.2 and 7.4) as ruled by the Panel should not be upheld.

Novo Nordisk submitted that against this background it was understandably concerned and surprised about the two breaches of Clause 2 that had been ruled where the substance of the breaches were Clauses 3.2 and 22.1, particularly given that the MHRA was evidently very satisfied with the quality of the materials (shown by the unusually short pre-vetting period).

Novo Nordisk submitted that such significant discrepancies between the MHRA and the PMCPA harmed the industry and were contrary to the spirit of the Memorandum of Understanding.

**Media Backgrounder Package/Press Releases**

Novo Nordisk agreed that complaints should be judged on the information provided by Novo Nordisk rather than the content of any articles and so it confined its arguments and remarks to the content of the media backgrounder package and the press releases. However, Novo Nordisk challenged the Panel's decision that each part of the package should be considered wholly in isolation. The media backgrounder package should be scrutinized in its entirety as it was provided to journalists as a complete pack containing the relevant press release (medical media or lay press) and the backgrounders. The press would have been fully aware of the licensed indication of Victoza, as it was clearly highlighted at the beginning of the press releases and was placed on the product-specific backgrounder ('Victoza (liraglutide)').

As these materials were prepared for the launch of Victoza, Novo Nordisk was no longer using the press releases and media backgrounder package that were the subject of these rulings.

Novo Nordisk noted that the Panel considered that inappropriate significance was given to additional benefits as opposed to licensed indications. Novo Nordisk submitted that proper emphasis was placed on Victoza's licensed indication in the backgrounders. The 'Victoza (liraglutide)' backgrounder clearly stated the licensed indication immediately between the title and the heading immediately below ('The importance of type 2 diabetes risk factors'). Thus, in the Victoza (liraglutide) backgrounder, the references to the impact of liraglutide on weight loss, reduction in systolic blood pressure and improved beta-cell function – the additional benefits – (in the first and fourth paragraphs of page 1) immediately followed the statements as to the licensed indication. Similarly, in the 'Incretins' backgrounder under the heading 'Victoza (liraglutide)' it was clearly stated initially that 'Liraglutide is a once-daily human GLP-1 analogue. Liraglutide lowers glucose levels by stimulating the release of insulin only when glucose levels become too high'. Only in the immediately following sentence was there reference to 'weight loss, reduction in systolic blood pressure (SBP) and improved beta cell function'. In addition, the media backgrounder package of which this backgrounder was a part, should be read as a whole.

Novo Nordisk submitted that it was inappropriate and unjust for the Panel to rule a breach of Clause 3.2 of the Code when the same item was approved

by the MHRA as being in compliance with Regulation 3A(1) of the Advertising Regulations and Paragraph 4.3 of the Blue Guide. Therefore Novo Nordisk denied that the media backgrounder package as a whole and the Incretins' and 'Victoza (liraglutide)' backgrounders were in breach of Clause 3.2.

Novo Nordisk noted that the Panel considered that the weight claims in the 'Incretins' backgrounders could not be substantiated because the weight finding related only to certain combinations of liraglutide and oral antidiabetic agents, the weight loss data was not quantified and the majority of patients was likely to remain overweight/obese after the weight loss.

Section 5.1 of the Victoza SPC stated that liraglutide in combination with metformin, metformin and glimepiride and metformin and rosiglitazone was associated with sustained weight reduction of 1.0 to 2.8kg. These combinations covered three out of four potential licensed combinations. The only combination in which liraglutide was revealed to be weight neutral (0.23kg weight loss with 1.8mg and 0.32kg weight gain with 1.2mg) was the combination with glimepiride. Even in this latter combination the use of liraglutide was not associated with clinically significant weight gain. Although the 0.32kg weight gain on the 1.2mg arm was statistically significantly different compared with placebo (-0.1kg), this difference could hardly be considered as clinically relevant.

Novo Nordisk noted that in the LEAD trials liraglutide was investigated in eight study arms and in seven either 1.8mg or 1.2mg was associated with statistically significant weight loss Marre *et al* (LEAD 1), Nauck *et al* (LEAD 2), Zinman *et al* (LEAD 4) and Russell-Jones *et al* (LEAD 5), 2009. Novo Nordisk believed that on the basis of this evidence the overall claim of 'weight loss' was justified and appropriate.

As to the Panel's concern as to quantification of weight loss, Novo Nordisk submitted that the quantification of the observed weight losses with liraglutide throughout the LEAD trials which the Panel remarked was missing from the 'Incretins' backgrounder, could be found in the product related backgrounder of 'Victoza (liraglutide)'. It was inappropriate to rigidly consider each backgrounder within the media backgrounder package in isolation, as they were all provided together as a single pack.

Novo Nordisk submitted that clinically no medicine would be expected to normalize the patient's body weight in order to make a favourable weight claim. Such an impact was not even required by the regulatory authorities to support an antiobesity indication.

Novo Nordisk noted that whilst Clauses 7.2 and 7.4 of the Code and Regulations 3A(2) and (3) of the Advertising Regulations/Paragraph 4.3 of the Blue guide were not entirely equivalent, pre-vetting against such requirements took place.

On the basis of the above, Novo Nordisk therefore disagreed with the Panel that the weight claim in the 'Incretins' Backgrounder could not be substantiated and was therefore in breach of Clause 7.4 of the Code.

Novo Nordisk noted that the Panel had considered that the 'Victoza (liraglutide)' backgrounder implied that all patients using Victoza lost weight and alleged that the weight gain data relating to the 1.2mg dose as evidenced by the SPC was not shown. Novo Nordisk submitted that it did not understand the Panel's objection here as the 'Victoza (liraglutide)' backgrounder clearly stated in relation to Marre *et al* (LEAD 1) at paragraph 5 on page 2 that: 'Changes in body weight with liraglutide 1.2mg (+0.3kg, baseline 80kg) were less than with rosiglitazone (+2.1kg, $p<0.001$, baseline 80.6kg)'. The balance of medical evidence was sufficient enough to make a favourable weight claim, as discussed above.

Novo Nordisk therefore disagreed with the Panel that the 'Victoza (liraglutide)' backgrounder was in breach of Clauses 7.2, 7.3, 7.4 and 7.10 of the Code.

Novo Nordisk noted that the Panel considered that the data regarding weight loss in both the press releases were not capable of substantiation, and therefore in breach of Clause 7.4 of the Code. The Panel also ruled a breach of Clause 7.3.

With respect to the breach of Clause 7.4 Novo Nordisk reiterated its comments in relation to the above, indicating that the overall medical evidence substantiated the weight loss claim in relation to liraglutide. Whilst Clauses 7.2 and 7.4 of the Code and Regulations 3A(2) and (3) of the Advertising Regulations/Paragraph 4.3 of the Blue Guide were not entirely equivalent, Novo Nordisk noted that pre-vetting against such requirements took place. As to the ruling of a breach of Clause 7.3, in that it related to comparisons, Novo Nordisk did not understand its relevance and appealed on that basis.

Novo Nordisk noted that the Panel was concerned that the quotation from Professor Barnett ('… may benefit from weight loss') implied that patients would lose weight with liraglutide resulting in being no longer obese/overweight, and was therefore unsubstantiated. Novo Nordisk strongly disagreed with this interpretation. Making a favourable weight claim about a compound did not mean that all patients using the medicine would, in fact, lose weight, or, indeed, that the weight loss would be sufficient to make them no longer obese/overweight. This was not a realistic clinical expectation. Furthermore, as noted above, interpreting such a claim as a statement to the effect that patients would no longer be overweight/obese was inappropriate. No health professionals would reasonably expect such an impact. A better and more realistic view was that the above wording (particularly use of the word

'may') would simply be interpreted as meaning that some patients would lose weight. As explained above, this claim could be substantiated and Novo Nordisk therefore reiterated its arguments in that respect.

Novo Nordisk submitted that, whilst Clauses 7.2 and 7.4 of the Code and Regulations 3A(2) and (3) of the Advertising Regulations/Paragraph 4.3 of the Blue Guide were not entirely equivalent, it noted that pre-vetting against such requirements took place. Therefore, Novo Nordisk disagreed with the Panel that using the quote from the health professional in the press releases was in breach of Clause 7.4 of the Code.

Novo Nordisk noted that the Panel considered the press releases misleading and inconsistent with the Victoza SPC with regard to the licensed indication. Novo Nordisk submitted that it did not understand how the press releases could be misleading by implying unlicensed indications for liraglutide since there were prominently highlighted boxes clearly specifying the licensed indication immediately under the headline of both items. Furthermore the press releases went onto describe the mechanism by which liraglutide reduced blood glucose levels (the licensed indication) and only referred in the paragraph below under the sub-heading 'Addition benefits' to the observed weight loss, systolic blood pressure reduction and beta-cell function improvement as additional benefits of liraglutide.

Novo Nordisk argued that it was inappropriate and unjust for the Panel to rule a breach of Clause 3.2 of the Code when the same item was approved by the MHRA as being in compliance with Regulations 3A(1) of the Advertising Regulations and Paragraph 4.3 of the Blue Guide. In addition, whilst Clauses 7.2 and 7.4 of the Code and Regulations 3A(2) and (3) of the Advertising Regulations/Paragraph 4.3 of the Blue Guide were not entirely equivalent, Novo Nordisk noted that pre-vetting against such requirements took place. Thus on the basis of the above and the previously detailed arguments related to the Media Backgrounder Package, Novo Nordisk disagreed with the Panel that the press releases were in breach of Clauses 3.2 and 7.2 of the Code.

Novo Nordisk submitted that it was inappropriate and unjust for the Panel to rule a breach of Clause 22.1 of the Code when the MHRA had considered that the same item complied with, *inter alia*, Paragraph 5.2 of the Blue Guide.

**COMMENTS FROM LILLY**

Lilly submitted that Novo Nordisk was unreasonable to assert that each part of the package should not be considered in isolation by the Code. This presupposed that all journalists would necessarily and diligently scrutinize the entire content of the media backgrounder package and not simply elect to read what was of interest to them.

Lilly noted that Novo Nordisk clearly acknowledged that only three out of the four potential licensed combinations of liraglutide were in fact discussed. Indeed, Novo Nordisk appeared to have elected to selectively omit information indicating the weight gain associated with liraglutide 1.2mg plus glimepiride on the premise that this was a 'weight neutral combination' and that the statistically significant difference vs placebo 'could hardly be considered to be clinically relevant'. The cherry-picking of the data, for what was the main maintenance dosage of liraglutide, misled readers by omission and was inaccurate.

Lilly stated that it was important to appreciate that the material was also aimed at consumer journalists and audiences. Whilst Lilly acknowledged the benefits of weight loss associated with the GLP-1 analogues and the validity of discussing this additional benefit in the management of type 2 diabetes in a balanced and fair manner, the materials at issue implied that liraglutide was indicated as a weight loss treatment over and above that for glycaemic control, which was not so. The latter, alongside some of the exaggerated discussion of the magnitude of the weight loss associated with liraglutide, could reasonably lead a consumer audience to believe that liraglutide could normalise body weight or reduce it to an extent that altered their cardiovascular risk in a significant and/or meaningful manner.

**APPEAL BOARD RULING**

The Appeal Board noted that both Novo Nordisk's written submission and its representatives at the appeal referred to pre-vetting of some materials by the MHRA. The Chairman noted that pre-vetting by the MHRA did not preclude consideration of a complaint under the Code nor did it preclude rulings of breaches of the Code. This was conceded by the company representatives.

The Appeal Board noted from the Novo Nordisk representatives at the appeal that all of the media backgrounders were provided as a package with a copy of the Victoza SPC in a single folder. This had not been clear in Novo Nordisk's previous submissions. A copy of the folder had not been provided to the Panel or the Appeal Board.

The Appeal Board noted that the paragraph at issue in both the 'Victoza' and 'Incretins' backgrounders stated that 'Victoza lowers glucose levels by stimulating the release of insulin only when glucose levels become too high. Victoza's impact on HbA1c control, weight loss, reduction in systolic blood pressure (SBP) and improved beta cell function has been consistently demonstrated throughout the phase 3a LEAD (Liraglutide Effect and Action in Diabetes) trials'.

The Appeal Board considered that the first sentence set out the licensed indication for Victoza. The following sentence then referred to some of the additional benefits of Victoza, as discussed in the

SPC. The Appeal Board did not consider that the statement at issue implied that Victoza could be prescribed as much for its additional benefits as for its licensed indications. The Appeal Board considered that the statement was not inconsistent with the Victoza SPC and ruled no breach of Clause 3.2 of the Code. The appeal on this point was successful.
The Appeal Board noted that the 'Incretins' backgrounder did not quantify weight loss. Given the association between excess body weight and type 2 diabetes it was important that potential weight loss was quantified. In that regard the 'Incretins' backgrounder was not capable of substantiation and the Appeal Board upheld the Panel's ruling of a breach of Clause 7.4. The appeal on this point was unsuccessful.

The Appeal Board noted that unlike the 'Incretins' backgrounder the 'Victoza' backgrounder provided some quantative data on weight changes from Marre *et al* (LEAD 1), Nauck *et al* (LEAD 2) and Zinman *et al* (LEAD 4). Buse *et al* (LEAD 6) was also mentioned but detailed data was not included. Weight change ranged from -2.8kg (1.8mg liraglutide plus metformin, LEAD 2) to +0.3kg (1.2mg liraglutide, LEAD 1). Weight loss was reported in three of the four studies included. The Victoza SPC stated that weight loss ranged between 1 and 2.8kg. The Appeal Board did not consider that the 'Victoza' backgrounder implied that every patient on Victoza would lose weight. The Appeal Board noted that whilst the 'Victoza' backgrounder did not reflect the totality of the weight change data sufficient information was given such that the backgrounder was not misleading, exaggerated or incapable of substantiation on this point. The Appeal Board ruled no breach of Clauses 7.2, 7.3, 7.4 and 7.10. The appeal on this point was successful.

The Appeal Board noted that both the medical and the lay press releases stated under a section headed 'Additional benefits' that 'Victoza can help patients achieve weight loss by increased satiety and delayed gastric emptying, and thus reduce caloric intake'. This was described as an important factor in treating type 2 diabetics as many were overweight. The Appeal Board noted that the press releases each included a section on 'Comparative Studies' which detailed the results of Buse *et al* (LEAD 6) in which a direct comparison between Victoza and exenatide found that both treatments led to a 3kg weight loss during the 26-week study. No further details of weight loss/gain were quantified. The Appeal Board noted that the Victoza SPC stated that weight loss ranged between 1.0 and 2.8kg. The Appeal Board noted that Novo Nordisk had accepted the Panel's ruling of a breach of Clause 7.2 regarding the data on weight loss in the press releases. Notwithstanding this ruling the Appeal Board did not consider that overall the data on weight in the press releases was incapable of substantiation or constituted a misleading comparison; the Appeal Board ruled no breach of Clauses 7.3 and 7.4. The appeal on this point was successful.

The Appeal Board noted that the health professional's statement in the press releases that '…patients with type 2 diabetes can be confident they are controlling their blood sugar, and may benefit from weight loss. This is an important advance for patients type 2 diabetes, many of whom are overweight' appeared in the 'additional benefits' section of both press releases. The Appeal Board noted that Novo Nordisk had accepted the Panel's ruling of a breach of Clauses 7.2, 7.3 and 7.10 on this point. The Appeal Board noted that Victoza was indicated for the treatment of type 2 diabetes and that its SPC referred to weight loss. The Appeal Board did not consider that the claim was incapable of substantiation and no breach of Clause 7.4 was ruled. The appeal on this point was successful.

The Appeal Board did not consider that the press releases were either inconsistent with the SPC or misleading about the licensed indication. The Appeal Board ruled no breaches of Clauses 3.2 and 7.2. The appeal on this point was successful.

The Appeal Board did not consider that the tone of the press releases was inappropriate. The Appeal Board noted its rulings regarding weight change. The Appeal Board did not consider that the claims in effect had turned the press release into an advertisement for a prescription only medicine. The Appeal Board ruled no breach of Clause 22.1. The appeal on this point was successful.

**2 Article on Telegraph.co.uk 'New drug for type 2 diabetes helps with weight loss'**

**COMPLAINT**

Lilly referred to its comments in point A1 above. The title 'New drug for type 2 diabetes helps with weight loss', the subheading 'A new once a day drug for type 2 diabetes which also helps patients lose weight and control blood pressure, has been launched in Britain' and the content and quotations from the Novo Nordisk spokespersons invited the reader to understand that liraglutide was licensed in the UK both as an anti-obesity treatment and an antihypertensive in patients with type 2 diabetes.

The overarching emphasis on obesity and the weight reduction benefit associated with liraglutide was unbalanced and misleading. Again, the implicit message was that obesity, per se, was the primary and only cause of type 2 diabetes and that the primary goal of liraglutide treatment was to impact this, as opposed to achieving glycaemic control in combination with other antidiabetic agents.

Unqualified and sweeping generalisations such as '… the traditional drugs used to control [type 2 diabetes] often encourage more weight gain' misled the reader and disparaged products such as Byetta, which was associated with an additional weight loss benefit in the management of glycaemic control in type 2 diabetes, and metformin which, at worst, had

a neutral impact on weight. This statement was also an implied criticism of insulin therapy which, as per Lilly's previous comments, might be an unavoidable therapeutic option for many patients with type 2 diabetes.

This type of message was irresponsible and might alarm a lay audience. Indeed this particular quotation suggested that current National Institute for Health and Clinical Excellence (NICE) guidelines, which recommended the use of metformin, sulphonylureas and insulin, should be ignored in preference to using liraglutide. Again, statements such as '[liraglutide] is an important advance' exaggerated the facts and misled by suggesting that liraglutide represented an important novel therapeutic advance with respect not only to weight reduction benefits but also glycaemic control. The precise importance or advance conferred by the availability of liraglutide was difficult to gauge given that it was the second GLP-1 analogue to be marketed and that both the injectable dosage form and the once-daily dosage were neither unique nor novel with respect to other currently available injectable and oral antidiabetic products.

Lilly alleged that the article effectively promoted liraglutide and advertised its weight reduction and blood pressure lowering benefits whilst largely ignoring the most important message for this readership which was that the major problem affecting type 2 diabetics was the need to achieve adequate glycaemic control in order to delay the onset of long-term complications such as heart disease; this would be consistent with the SPC.

The likely promotional nature of the media and speaker briefing materials was also evidenced by three separate mentions of the brand name and the statement that 'It costs £78.48 per month'. This information was not relevant to a consumer audience and suggested that Novo Nordisk's media briefing materials, which should not be promotional, included prescribing information which was contrary to the Code. Notwithstanding the latter, it was also incomplete and indirectly invited the reader to consider the relative cost of liraglutide compared with other antidiabetic treatments. It was implied that liraglutide could be used as monotherapy.

Again, this particular article and the Novo Nordisk spokespersons did not present a relevant and balanced discussion of the risks and benefits associated with liraglutide. The statement that '… [liraglutide] reduces the likelihood of hypoglycaemic attacks' was misleading by omission and minimised the very common or common occurrence of hypoglycaemia when liraglutide was combined with glimepiride, metformin and glimepiride, or metformin and rosiglitazone as indicated in the SPC.

Lilly alleged that this article and the quotations attributed to opinion leaders (one of whom was from a named patient organisation) were based on misleading, unbalanced and inaccurate media and speaker briefing materials developed by Novo Nordisk and therefore constituted a breach of Clauses 3.2, 7.2, 7.3, 7.4, 7.9, 7.10, 8.1, 12.1, 22.1, 22.3 and 22.5.

**RESPONSE**

Novo Nordisk referred to its response at point A1 above as to the materials provided by Novo Nordisk, and the fact that Novo Nordisk did not have any editorial control with regard to the final article.

Nevertheless, Novo Nordisk submitted that the title of the article 'New drug for type 2 diabetes helps with weight loss' was not ambiguous and did not imply that liraglutide was a licensed anti-obesity treatment. It was a new medicine, and in line with the SPC it could help with weight loss.

Novo Nordisk believed that health professionals would agree with the statement that 'traditional drugs used to control [type 2 diabetes] often encourage more weight gain'. The statement referred to classic agents such as sulphonylureas, thiazolidinediones and insulin which health professionals widely acknowledged to be associated with weight gain.

Novo Nordisk disagreed with Lilly that the article invited the reader to ignore the current NICE recommendations. Lilly had not asserted how the article invited the readers to ignore the current NICE guidelines, and which parts of the NICE guidelines the reader was invited to ignore. Further, Novo Nordisk considered that liraglutide represented a novel therapeutic advancement in the treatment of type 2 diabetes, as the other currently available GLP-1 analogue, exenatide could not be used once-daily in contrast to liraglutide.

Novo Nordisk did not agree that the article invited the reader to understand that liraglutide was licensed as an anti-obesity and antihypertensive agent for patients with type 2 diabetes, for the reasons set out above. It therefore denied that this article was in breach of the Code as alleged.

**PANEL RULING**

The Panel noted its comments and rulings in point A1 above regarding the press pack which it considered also applied here. These rulings were appealed.

The Panel had not been informed whether or not the named patient organisation had attended the launch or what materials Novo Nordisk had provided to that organisation. The Panel's rulings in Point A1 above related to Novo Nordisk's press pack.

The opinion leader from the patient organisation, quoted in the article at issue, was not a Novo Nordisk spokesperson. The Panel decided that on the information before it Novo Nordisk was not

responsible under the Code for these comments. No breach of the clauses of the Code cited by Lilly (Clauses 3.2, 7.2, 7.3, 7.4, 7.9, 7.10, 8.1, 12.1, 22.1, 22.3 and 22.5) was ruled in that regard.

**APPEAL BY NOVO NORDISK**

Novo Nordisk submitted that this article was, in part, a consequence of the Media Backgrounder Package addressed in A1 above and its position taken in A1 was repeated in relation to this article.

**COMMENTS FROM LILLY**

There were no comments from Lilly.

**APPEAL BOARD RULING**

The Appeal Board noted its comments and rulings in Point A1 above regarding the press pack which it considered also applied here.

**3 Television interview, ITV, This Morning, 15 July 2009**

**COMPLAINT**

Lilly alleged that the comments in this interview were based upon inaccurate and misleading media and speaker briefing materials provided by Novo Nordisk.

The individual concerned was alleged to be a Novo Nordisk spokesperson as evidenced by quotations attributed to him which he made on behalf of Novo Nordisk at the launch meeting. In the interview of 15 July 2009 his comments effectively promoted liraglutide to consumers. Statements such as '… the experts are saying it's going to transform the management of diabetes' exaggerated the facts and raised unfounded hopes and expectations of successful treatment with liraglutide. Further, comments from the programme's co-presenter such as 'Victoza it's called, if that's appropriate for you, and you must go and talk to the doctor about it' encouraged members of the public to ask doctors to prescribe liraglutide. This discussion of liraglutide was unbalanced and invited an unfair and misleading comparison by highlighting the positive benefits associated with liraglutide compared with insulin therapy. Insulin therapy was discussed as a 'problem', unlike liraglutide, and to emphasise this point viewers were told about hypoglycaemia, meal-time dosing restrictions and weight gain associated with insulin. A lay audience could reasonably surmise that liraglutide was better than insulin therapy and obviated the need for insulin therapy in all patients with type 2 diabetes. Indeed, the latter was further emphasised by the significant focus on the weight and blood pressure reduction benefits associated with liraglutide which when discussed, elicited an exclamation of 'Wow!' from the co-presenter who was a well known proponent of the weight loss and dieting lobby.

Lilly alleged that this interview was based on misleading, unbalanced and inaccurate media and speaker briefing materials developed by Novo Nordisk and therefore constituted a breach of Clauses 3.2, 7.2, 7.3, 7.4, 7.9, 7.10, 8.1, 12.1, 22.1, 22.2, 22.3 and 22.5.

**RESPONSE**

Novo Nordisk referred to the comments in Point A1 with regard to the content of the interviews by the independent health professionals and the quotations detailed within the above publications made by external health professionals.

Novo Nordisk had no input into the content of the interviews or the articles referred to above, other than provision of the briefing packs.

Novo Nordisk was committed to ensure the extensive media backgrounder press packs and the press releases, for the medical media and for lay press provided accurate information about type 2 diabetes, the company and the licensed indication for liraglutide, to ensure that the information provided to journalists was accurate, balanced and fair and not 'inaccurate and misleading' as alleged by Lilly. An external agency assisted Novo Nordisk and the content was pre-vetted by the Medicine and Healthcare products Regulatory Agency (MHRA). Amendments were requested by the MHRA, and these were made before the materials were released.

Novo Nordisk submitted that these activities were not in breach as alleged.

**PANEL RULING**

The Panel noted its comments and rulings in point A1 above regarding the press pack which it considered also applied here. These rulings were appealed.

The interview in question was with a media doctor who had spoken at the launch meeting and had provided interviews. It did not appear that his appearance on the programme was specifically due to his role with Novo Nordisk at the launch of Victoza. It appeared to be due to his regular role as the programme's commentator on medical matters. The position was unclear. The Panel considered that given Novo Nordisk had selected the individual as a speaker in relation to the launch of Victoza it was difficult to argue that, on this occasion, when speaking about Victoza, he was entirely independent from the company. The Panel considered that the item in question placed undue emphasis on the weight reduction effects of Victoza and this was extremely concerning. Novo Nordisk had provided much information about the product to the individual who was a spokesperson for Novo Nordisk at its press conference and follow up interviews. The Panel was extremely concerned about what was said in the interview and decided that the comments were covered by the rulings in A1 above. These rulings were appealed.

**APPEAL BY NOVO NORDISK**

Novo Nordisk submitted that this interview was, in part, a consequence of the Media Backgrounder Package addressed in A1 above and its position taken in A1 was repeated in relation to this interview.

**COMMENTS FROM LILLY**

There were no comments from Lilly.

**APPEAL BOARD RULING**

The Appeal Board noted its comments and rulings in Point A1 above regarding the press pack which it considered also applied here.

Given Novo Nordisk's submission the Appeal Board questioned the briefing. Nonetheless, the Appeal Board made no additional ruling on the comments of the individual, who it considered had acted as a Novo Nordisk spokesperson, as it considered that the matter was covered by its reference to Point A1 above.

**4 Radio interviews, BBC Radio Ulster, Good Morning Ulster, 7 July 2009**

**COMPLAINT**

Lilly stated that from the outset, the content of this consumer programme promoted and advertised the weight reduction benefits associated with liraglutide. The discussion opened with a health professional stating that '… common discomforts for diabetes include the weight gain much of their medication can cause ...' and was followed by 'Hopefully though not any more, a new drug called Victoza for people suffering with type 2 diabetes is being released today'. This health professional also emphasised that liraglutide '…will help patients with diabetes control their weight which is a major problem'. Again, wording such as 'This treatment really is a major step forward ...' exaggerated the facts and misled by suggesting that liraglutide represented an important novel therapeutic advance with respect not only to weight reduction benefits but also glycaemic control. The step forward offered by liraglutide was difficult to gauge given that it was the second GLP-1 analogue to be marketed and the fact that both the injectable dosage form and the once-daily dosage were neither unique nor novel with respect to other currently available injectable and oral antidiabetic products. The implication was that liraglutide offered benefits that were currently unavailable for example with products such as Byetta.

Comments from the health professional sought to engender confidence in the safety of liraglutide by exaggerating that the testing and development of liraglutide had '… been one of the most extensive programmes of development that we have seen in diabetes ...'; this claim was disparaging, was unsubstantiated and misled the lay audience by suggesting that this was a quality standard not applicable to, or achieved by, other licensed antidiabetic agents.

The comments from the health professional did not set out a relevant and balanced discussion of the risks and benefits associated with liraglutide. The statement that '… the risk therefore of developing low blood sugars or hypoglycaemia which many people with diabetes will have heard about is extremely low' was misleading by omission.

Given the intended audience the health professional did not mention the safety and tolerability of this new treatment particularly with regard to the incidence of gastrointestinal side effects, which occurred very commonly, and hypoglycaemia which occurred commonly or very commonly when liraglutide was used in combination with glimepiride, metformin and glimepiride or metformin and rosiglitazone; this would have provided balance to the interview.

The health professional discussed that 'The early studies that we've seen and the early data that we have suggest that maybe [liraglutide] might do something about the progression of the disease. We know that type 2 diabetes doesn't stand still, it's a condition that gets worse year on year, and there's increasing evidence to suggest that this new type of treatment may actually delay that progression' and '... it seems as though this new treatment, Victoza, may preserve beta cell function and may even improve beta cell function and therefore stop the condition progressing and stop the likelihood of patients needing to go onto more complex treatment such as insulin'. The assertion that liraglutide could stop the condition progressing and the discussion of the putative mechanisms which might underlie the observations from the early studies constituted the off-licence promotion of liraglutide to the public. Lilly noted that Byetta was the first-in-class of this type of treatment and not liraglutide, as was implied in this statement.

Lilly alleged that this interview and the quotations attributed to the health professional were based on misleading, unbalanced and inaccurate media and speaker briefing developed by Novo Nordisk and therefore constituted a breach of Clauses 3.2, 7.2, 7.3, 7.4, 7.9, 7.10, 8.1, 12.1, 22.1, 22.3 and 22.5.

**RESPONSE**

Novo Nordisk referred to its response in point A3.

**PANEL RULING**

The Panel noted its comments and rulings at point A1 above regarding the press pack which it considered also applied here. These rulings were appealed.

The interview in question was with a health professional who had been briefed by Novo Nordisk

to give interviews in relation to the Victoza launch. The Panel was concerned that the health professional had stated that Victoza 'will also help them control their weight which is a major problem'. The spokesperson stated that Victoza was a major step forward. The Panel queried whether this was so. It was the second GLP-1 medicine to be launched but the first to be administered once a day. The Panel considered that Novo Nordisk was responsible under the Code for the comments made by the health professional. The Panel considered that the allegations about what was said by the health professional with regard to Victoza's effect on weight and it being a major advance in therapy were covered by its rulings in point A1 above.

The Panel noted that the health professional had stated that Victoza had undergone 'one of the most extensive programmes of development that we've seen in diabetes, probably well over ten years now that's …'. In the Panel's view this statement implied that Victoza had undergone a more extensive development programme than other antidiabetic medicines. There was no information before the Panel to substantiate this implied comparison. The Panel considered that the statement was misleading and that it disparaged other medicines. Breaches of Clauses 7.2, 7.3, 7.4 and 8.1 were ruled.

The Panel considered that the health professional's statement that the risk of developing hypoglycaemia was extremely low was misleading with respect to the safety of Victoza. The SPC stated that hypoglycaemia was common and very common when Victoza was used in combination with a sulphonylurea. The Panel ruled a breach of Clauses 7.2 and 7.9 of the Code. The Panel further noted that in response to the question 'And how long has it been trialled for? There's a lot of concern sometimes about side-effects' the health professional did not refer to the side effect profile of Victoza, in particular he did not discuss the common or very common gastrointestinal effects of the medicine. The Panel considered that the answer to the question was misleading by omission and ruled a breach of Clause 7.2.

The Panel noted that the health professional had stated that Victoza might stop type 2 diabetes progressing and stop the likelihood of patients needing to go onto insulin. There was no data before the Panel to show that this was so. Although beta-cell function improved with Victoza it had not been demonstrated that, patients would not need to progress onto insulin therapy. The Panel considered that the statement was misleading and exaggerated. A breach of Clauses 7.2 and 7.10 was ruled.

**APPEAL BY NOVO NORDISK**

Novo Nordisk submitted that this interview was, in part, a consequence of the Media Backgrounder Package addressed in A1 above and its position taken in A1 was repeated in relation to this interview.

Novo Nordisk did not appeal any of the specific rulings with respect to these radio interviews.

**COMMENTS FROM LILLY**

There were no comments from Lilly.

**APPEAL BOARD RULING**

The Appeal Board noted its comments and rulings in Point A1 above regarding the press pack which it considered also applied here.

**5 Article in The Pharmaceutical Journal 'Liraglutide launched as new option for uncontrolled diabetes'**

**COMPLAINT**

Lilly alleged that this article was aimed at health professionals and was evidently based on the launch briefing in London. Lilly alleged that the inaccurate, misleading and unbalanced reporting of liraglutide with particular regard to discussion of the incidence of severe hypoglycaemia and weight loss were the result of inaccurate, misleading and promotional media and speaker briefing materials provided by Novo Nordisk.

The statement that liraglutide was '… the first once-daily human glucagon-like peptide-1 (GLP-1) analogue to be made available' misled the reader by omission. In the absence of any mention of Byetta the impression created by this wording was that liraglutide was the first licensed product in this particular class.

One of the health professional's quoted in this article was reported to have claimed that when liraglutide was used with metformin 'severe hypoglycaemia is virtually unheard of' and 'almost impossible' because of the medicine's glucose-dependant action. This statement was promotional in nature, selective, misled by omission and exaggerated the relevance and importance of clinical trial observations to what might be observed in real-life clinical practice. There was also no reference to the equally important observation that hypoglycaemia occurred commonly or very commonly when liraglutide was used in combination with glimepiride, metformin and glimepiride or metformin and rosiglitazone.

In the absence of this clarification and given the credibility and gravitas lent to this opinion by a respected physician, readers might reasonably assume that the risk benefit associated with liraglutide in combination with other antidiabetics was similar. Indeed this focus on severe hypoglycaemia served to obfuscate from a discussion of the incidence of gastrointestinal side-effects which occurred very commonly and were particularly important with regard to GLP-1 receptor agonists. This was a breach of Clauses 7.2, 7.3 and 7.9.

The health professional was also reported to have stated that 'The other big advantage, which patients really appreciate, is if you use this drug in combination with metformin you're getting very nice weight loss, which you are noticing already at two weeks and continues at 26 weeks compared with sulphonylurea combination where you are getting weight gain. And that difference is 3.6kg ...'. Again, in the absence of any discussion of the glycaemic control associated with liraglutide, this statement placed undue emphasis on the benefit of weight loss and suggested that this should be the primary therapeutic consideration. Further, the claim that patients would really appreciate this was pure supposition that required substantiation.

This statement was misleading, inconsistent with the SPC and did not represent the balance of evidence with respect to the specific numerical benefit in weight loss reported. This claim referred to data from a single study that had been cherry-picked from a single 26 week study to compare the efficacy and safety of liraglutide, glimepiride and placebo, all in combination with metformin in patients with type 2 diabetes; patients were randomised to receive once-daily liraglutide (0.6, 1.2, or 1.8mg/day) in combination with metformin, metformin monotherapy, or combination therapy of metformin and glimepiride. This claim misled by omission and exaggerated the results in the absence of any indication of the baseline body weight and BMI by which the implied clinical and statistical significance of the reductions referred to could be assessed (Lilly referred to point B3 below with regard to item number UK/LR/0409/0079).

The wording of this statement also suggested that the weight loss observed was sustained beyond 26 weeks; this could not be substantiated. Further, it was not clear that the reported weight loss referred to a mean observed only with the 1.2mg dosage of liraglutide and not the 0.6mg dose that this, all embracing, statement implied. This unqualified statement also misleadingly suggested that this comparison of liraglutide was with all available sulphonylureas and not specifically in combination with glimepiride.

Further, selectively promoting the result from a single study of liraglutide was misleading and exaggerated the benefits of liraglutide with regard to the weight loss benefit observed in other studies and was inconsistent with the manner in which it was discussed in the liraglutide SPC. The latter stated that 'Victoza in combination with metformin, metformin and glimepiride or metformin and rosiglitazone was associated with sustained weight reduction over the duration of studies in a range from 1.0kg to 2.8kg'; this wording more appropriately and fairly represented the balance of evidence regarding the weight loss observed with different dosages of liraglutide when combined with other antidiabetic treatments.

Lilly alleged that this was in breach of Clause 3.2, 7.2, 7.3, 7.4 and 7.10.

**RESPONSE**

Novo Nordisk referred to its response in point A3.

**PANEL RULING**

The Panel noted its comments and rulings in point A1 above regarding the press pack which it considered also applied here. These rulings were appealed. The article quoted a health professional speaking at the launch meeting. Novo Nordisk had not commented on the accuracy of the quotations despite its responsibility for what was said. The Panel was concerned that statements that 'severe hypoglycaemia was virtually unheard of' and 'almost impossible' were inconsistent with the data in the SPC which referred to hypoglycaemia when liraglutide was combined with metformin and glimepiride as very common and as common when liraglutide was combined with metformin and rosiglitazone. The SPC stated that major hypoglycaemia had primarily been observed when liraglutide was combined with a sulphonylurea.

The Panel was also concerned that the statements regarding weight loss were inconsistent with the SPC.

The Panel considered that the allegations about what was said by the health professional were covered by its rulings in points A1 and A4 above. These rulings were appealed.

**APPEAL BY NOVO NORDISK**

Novo Nordisk submitted that this article was, in part, a consequence of the Media Backgrounder Package addressed in A1 above and its position taken in A1 was repeated in relation to this article.

**COMMENTS BY LILLY**

There were no comments from Lilly.

**APPEAL BOARD RULING**

The Appeal Board noted that the article in The Pharmaceutical Journal included the claim '… when liraglutide is used with metformin "severe hypoglycaemia is virtually unheard of" and "almost impossible" because of the drug's glucose-dependent action'. This claim was attributed to a health professional speaking at the Victoza launch meeting. The Appeal Board was concerned that the claim was inconsistent with the SPC, which referred to hypoglycaemia as very common when liraglutide was combined with metformin and glimepiride and as common when liraglutide was combined with metformin and rosiglitazone. The SPC stated that major hypoglycaemia had primarily been observed when liraglutide was combined with a sulphonylurea. The Appeal Board considered that the claim at issue was misleading and ruled breaches of Clauses 7.2 and 7.9. The appeal on this point was unsuccessful. The Appeal Board did not consider, however, that there

was a misleading comparison and therefore ruled no breach of Clause 7.3. The appeal on this point was successful.

The Appeal Board noted that the article quoted the health professional as stating that 'The other big advantage, which patients really appreciate, is if you use this drug in combination with metformin you're getting very nice weight loss, which you are noticing already at two weeks and continues at 26 weeks, compared with sulphonylurea combination where you are getting weight gain, and that difference is 3.6 kg'. The Appeal Board noted Section 5.1 of the Victoza SPC stated that Victoza in combination with metformin, metformin and glimepiride or metformin and rosiglitazone was associated with sustained weight reduction over the duration of the studies in a range from 1.0kg to 2.8kg. The Appeal Board noted its rulings in Point A1 above. It did not consider that the claim was inconsistent with the Victoza SPC and ruled no breach of Clause 3.2. The appeal on this point was successful.

However, the Appeal Board considered that the claim was misleading as it implied that all patients would experience weight loss at two weeks and that was not so and that the comparison of liraglutide plus metformin was with liraglutide plus all available sulphonylureas and not specifically in combination with glimepiride. The Appeal Board considered that the claim was misleading and ruled breaches of Clauses 7.2 and 7.3. The appeal on this point was unsuccessful. The Appeal Board noted that the Victoza SPC referred to weight reduction and thus it considered that the claim was capable of substantiation and ruled no breach of Clause 7.4. The appeal on this point was successful. However the Appeal Board considered that the claim was exaggerated. The Appeal Board ruled a breach of Clause 7.10. The appeal on this point was unsuccessful.

**6 Article in Clinical Pharmacist 'Liraglutide added to type 2 diabetes arsenal'**

**COMPLAINT**

Lilly alleged that this article, aimed at health professionals, was clearly based on the inaccurate and misleading Novo Nordisk press briefing. The article reported comments by a pharmacist regarding the results of new study data comparing liraglutide with exenatide published in the Lancet (Buse *et al* 2009) LEAD 6.

This open-label study involved adults with inadequately controlled type 2 diabetes on maximally tolerated doses of metformin, sulphonylurea, or both, who were stratified by previous oral antidiabetic therapy and randomly assigned to receive additional liraglutide 1·8mg once a day or Byetta 10mcg twice a day in a 26-week open-label, parallel-group, multinational study.

The primary outcome was change in HbA1c. The quotations attributed to the pharmacist failed to qualify that the outcome associated with liraglutide was specific only to the 1.8mg dosage; this was misleading by omission and exaggerated the benefits to imply that the results and comparison with Byetta were also applicable to the 0.6 or 1.2mg dosages of liraglutide. Further there was a failure to qualify and consider the limitations of the open-label study design with respect to the efficacy and safety outcomes reported.

This was in breach of Clauses 3.2, 7.2, 7.3, 7.4, 7.9, 7.10, 8.1, 12.1, 22.1, 22.3 and 22.5.

**RESPONSE**

Novo Nordisk did not refer to this article in its response.

**PANEL RULING**

The Panel noted that the pharmacist quoted in the article was not one of the spokespeople who Novo Nordisk had submitted that it had used at the launch of Victoza. The Panel did not know whether the health professional had been provided with a press pack. The Panel decided on the information before it that Novo Nordisk was not responsible under the Code for the comments attributed to the health professional. There was no evidence that Novo Nordisk had provided any material to the health professional. No breach of the clauses of the Code cited by Lilly was ruled.

The Panel noted that the article also referred to another health professional's comment at the launch briefing ie that when liraglutide was used with metformin 'severe hypoglycaemia is virtually unheard of'. The Panel considered that its ruling at point A4 of breaches of Clauses 7.2 and 7.9 with regard to the risk of developing hypoglycaemia applied here.

The Panel noted its comments in point A1 about the press materials and thus did not consider Lilly's allegations about the content of the article.

**7 Article in the British Journal of Cardiology 'Liraglutide: novel drug for type 2 diabetes launched' and general allegations**

**COMPLAINT**

Lilly alleged that this article, aimed at health professionals, was clearly based on the inaccurate and misleading Novo Nordisk press briefing. The article referred to the fact that Novo Nordisk described liraglutide as 'a revolutionary product' and that it worked in a unique way. Both these claims were exaggerated and could not be substantiated. The revolution or uniqueness offered by liraglutide was difficult to gauge given that it was a second-in-class GLP-1 receptor agonist and the fact that both the injectable dosage form and the

once-daily dosage were neither unique nor revolutionary with respect to other currently available injectable and oral antidiabetic products. It was implied that liraglutide offered benefits that were currently unavailable for example with products such as Byetta. The statement that liraglutide was the first once-daily human GLP-1 analogue for the treatment of type 2 diabetes was alleged to be misleading by omission. With no reference to Byetta it was implied that liraglutide was first licensed product in this particular class.

It appeared that the Novo Nordisk press and speaker briefing materials facilitated the promotion of generalised and unqualified statements, regarding the substantial lowering of fasting and postprandial glucose concentrations, overall reduction in HbA1c of up to 1-2%, the associated reduction in weight and systolic blood pressure of about 7mmHg observed during the extensive clinical development programme for liraglutide. The LEAD study programme comprised six different studies. These studies employed different designs, different dosages of liraglutide, various comparators and dosages of these and differing efficacy/safety outcomes amongst many other variables. These qualifications were important and their absence in the context of promotional claims misled by omission and exaggerated the facts. For example the quoted 2% reduction in HbA1c did not represent the balance of evidence from the LEAD studies. Similarly, the figure for the reduction in blood pressure did not reflect the lower end of the range of 2.3mmHg and thus overstated the clinical significance of this observation. Further, the absence of baseline study subject demographics misled with regard to the implied clinical and statistical significance of the outcomes discussed.

Lilly questioned the accuracy, appropriateness, objectivity and balance of the Novo Nordisk speaker briefing in light of some of the quotations. This was exemplified by a quotation attributed to a health professional that liraglutide works so well 'and ticks so many boxes that it was almost too good to be true'. This was an unqualified promotional claim that exaggerated the facts and could not be substantiated. Again, as discussed in point A5 above, such quotations misrepresented and minimised the risk of hypoglycaemia associated with liraglutide.

The same health professional also made the promotional claim that the posology and method of administration '… should improve patient compliance and, in turn, clinical outcomes'. This assertion could not be substantiated with respect to liraglutide and was conjecture and hypothesis. The health professional also stated that it would be 'incredibly disappointing' if primary care trusts (PCTs) were to restrict the use of liraglutide and not have it widely prescribed prior to the result of NICE Technology Appraisal which was due in 2010; clearly this was a position endorsed by Novo Nordisk. Lilly alleged that this was wholly irresponsible and entirely inconsistent with the requirement of pharmaceutical companies to establish good working relationships with partners within the NHS and the Department of Health (DoH) to support and encourage the rational and safe use of new 'black triangle' treatments.

Finally, a quotation attributed to another health professional with the article, stated that the introduction of liraglutide might well 'change the lives of many diabetic patients' for the better. This was an unqualified, exaggerated promotional claim that could not be substantiated. Further, it disparaged existing antidiabetic agents and suggested that they did not deliver a positive change or improvement to diabetic patients.

Given the serious nature of the matter Lilly alleged that the media activity undertaken by Novo Nordisk, through its agents and spokespersons represented a breach of Clauses 2 and 9.1.

Lilly also believed that the media activity constituted a breach of the MHRA Blue Guide on the Advertising and Promotion of Medicines in the UK, which prohibited the promotion of prescription only medicines to patients and the public.

Lilly noted that in its response, Novo Nordisk indicated that it had decided to share the 'relevant' parts of Lilly's complaint of 4 September 2009 with the health professionals mentioned in what was a confidential inter-company communication. This was entirely inconsistent with the tenet and spirit of Paragraph 5.2 of the Constitution and Procedure. Indeed, Lilly questioned why, in the spirit of openness and transparent discussions Novo Nordisk had only shared selected aspects of its extensive complaint detailing the misleading promotion of liraglutide with those health professionals. Lilly regarded this as a serious attempt by Novo Nordisk to tarnish Lilly's reputation. Lilly categorically refuted the allegation that its intention was to disparage any of the health professionals mentioned in its complaint. The latter simply highlighted examples of how these health professionals might have been informed by misleading and inaccurate media and speaker briefing materials developed by Novo Nordisk and/or its agent(s); or indeed were not briefed at all. Lilly considered that the serious and premeditated breach of the Constitution and Procedure by Novo Nordisk represented a breach of Clauses 2 and 9.1.

**RESPONSE**

Novo Nordisk referred to its response at point A3.

Novo Nordisk disagreed with Lilly's view that Novo Nordisk had gone against the spirit and tenet of Paragraph 5.2 of the Constitution and Procedure, which Lilly considered implied that inter-company communications must remain confidential between the parties [see last paragraph of complaint at Point A7 below]. Paragraph 5.2 did not state that

inter-company communications must remain confidential between the parties, nor was Lilly's correspondence marked 'Confidential'. Novo Nordisk considered it both reasonable and important for it to approach the health professionals about whom the allegations were made, in order to fully investigate the allegations, to ensure its response was both informed and accurate. Further, Lilly alleged that the independent health professionals were also liable for the misleading and inaccurate information provided during the interviews. As such, Novo Nordisk believed it had a duty to inform these health professionals as to the allegations made by Lilly.

**PANEL RULING**

The Panel noted that Lilly had made a number of allegations regarding the content of the article at issue but had not cited those clauses of the Code which it considered had been breached other than a general reference to its allegations in A5 that the risk of hypoglycaemia associated with liraglutide was misrepresented and minimised. In the absence of clearly cited clauses the Panel decided that it could not make any rulings. Nonetheless the Panel noted its comments above about the press pack and asked that Novo Nordisk be advised that it had similar concerns here.

With regard to Lilly's comments about the MHRA Blue Guide the Panel noted that it could only consider the allegations in relation to the Code and not the MHRA Blue Guide or UK law. Finally, the Panel did not consider that it was inconsistent with Paragraph 5.1 of the Constitution and Procedure for Novo Nordisk to provide the health professionals used at the launch with details of the complaint. The Panel had not been given details of what Novo Nordisk had provided to the health professionals. As a principle it was not necessarily unacceptable under the Code. The Panel considered that, in relation to this allegation, Lilly had not proven its complaint on the balance of probabilities. No breach of Clauses 2 and 9.1 was ruled.

Lilly had referred to the media activity in total and alleged breaches of Clauses 9.1 and 2.

With regard to these general allegations, the backgrounders referred to above and the press releases the Panel considered that high standards had not been maintained and a breach of Clause 9.1 was ruled. With regard to Clause 2, which was used as a sign of particular censure, the Panel considered that issuing misleading material to the press was a serious matter as was issuing a press release that advertised a prescription only medicine to the public. The Panel thus ruled a breach of Clause 2 which was appealed.

**APPEAL BY NOVO NORDISK**

Novo Nordisk noted that no breaches were ruled in respect of the specific article but the Panel ruled a breach of Clause 2 of the Code in relation to the Media Backgrounder Package generally.

Novo Nordisk noted that Clause 2 indicated the Panel's view of the gravity of the alleged breaches. However Novo Nordisk contended that as it had successfully dealt with several of the Panel's concerns on a point by point basis and the great majority of the specific allegations in relation to the Media Backgrounder Package were already approved under the MHRA pre-vetting procedure, it failed to see how the Panel could form this view. Accordingly, Novo Nordisk disagreed with the Panel that the Media Backgrounder Package or any component of it was in breach of Clause 2 of the Code.

Novo Nordisk submitted that its concern regarding the discrepancy between the Panel's ruling and the MHRA pre-vetting approvals was particularly relevant in the case of the Clause 2 ruling.

**COMMENTS BY LILLY**

There were no comments from Lilly.

**APPEAL BOARD RULING**

The Appeal Board noted its rulings above and that the company had accepted a number of rulings of breaches of the Code.

The Appeal Board was concerned that it did not have all the relevant material such as the press pack folder and the presentations given at the launch meeting. Although the Appeal Board had concerns about the material Novo Nordisk had provided it did not consider overall that these warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure. No breach of Clause 2 was ruled. The appeal on this point was successful.

**B Promotional Materials**

**1 Journal advertisement (UK/LR/0409/0087)**

The advertisement at issue was a double page spread. The illustration on the left hand page was of what readers would assume to be a male doctor's hand holding the roots and trunk of a small tree whose leaves and branches had been replaced by a multi-coloured lollipop. The right hand page was headed 'Do more than lower blood glucose' followed by a box containing the following:

'Once-daily Victoza, in combination with metformin and/or a sulphonylurea, impacts on multiple factors associated with type 2 diabetes providing from baseline

- Reductions in HbA1c

And in addition

- Reductions in weight
- Reductions in systolic blood pressure
- Improvements in beta-cell function.'

Immediately below the box, in small type, were the details of the licensed indications for Victoza.

**COMPLAINT**

Lilly alleged that the heading 'Do more than lower blood glucose' was misleading and inconsistent with the Victoza SPC; it invited the reader to consider that Victoza was licensed to achieve something clinically more significant than glycaemic control in combination with specific antidiabetic agents in type 2 diabetic adults. The prominence of the heading misled readers about the product's licensed indication and did not encourage rational use. The text box beneath the heading invited the reader to consider that '… Victoza, in combination with metformin and/or a sulphonylurea, impacts on multiple factors associated with type 2 diabetes providing from baseline ...' and further misled and reinforced the suggestion that Victoza was additionally indicated for '… reductions in weight, reductions in systolic blood pressure'. Given this, the heading clearly invited the reader to consider Victoza as a treatment for obesity and hypertension. The precise details of the Victoza indication only became apparent by reference to a footnote which followed various promotional claims and was not directly associated with the heading. Lilly noted the relatively small font of this footnote.

The wording, design and layout of this advertisement also invited a comparison with other antidiabetic agents, which like Victoza were all principally licensed to achieve glycaemic control, and suggested that Victoza offered something more than lowering blood glucose compared with these. The significant emphasis and discussion of the weight reduction benefits associated with Victoza only served to reinforce this suggestion.

The claims about reductions in weight and systolic blood pressure also misled by omission in the absence of any indication of the baseline by which the implied clinical and statistical significance of the reductions referred to could be measured. Further, whilst the claims about the reductions in weight and systolic blood pressure observed with Victoza were contextualised by reference to combination with 'a sulphonylurea', the important qualification that this specifically related to a combination with glimepiride, and not all sulphonylureas as was implied, was missing. Without the latter these claims misled readers by omission. This tendency to generalise, without appropriate qualification, efficacy claims in support of 'once-daily Victoza' misleadingly suggested that the reductions in weight, systolic blood pressure and HbA1c were clinically and statistically significant, applicable to all patients and had been observed with all three doses of Victoza when combined, as per indication, with metformin, glimepiride or rosiglitazone; this was not so.

The visual was also misleading and inconsistent with the SPC and the licensed indication. Whilst the depiction of type 2 diabetes by analogy to a 'lollipop tree' was not unreasonable, the depiction of the tree being entirely uprooted implied that Victoza could uproot type 2 diabetes and eliminate the illness completely; Victoza was not a cure for diabetes mellitus as was inferred by the visual. Notwithstanding the latter, the visual also implied that liraglutide delayed the progression of type 2 diabetes for which it was not licensed.

For the reasons outlined above Lilly alleged that this advertisement was in breach of Clauses 2, 3.2, 7.2, 7.3, 7.4, 7.8, 7.10, 8.1 and 9.1.

**RESPONSE**

Novo Nordisk stated that the majority of its promotional materials were pre-vetted and approved by the MHRA.

Novo Nordisk referred to a letter of 3 June 2009 from the MHRA which stated 'The indication should be included prominently in the main part of the stands and adverts to ensure that the audience is not misled as to the authorised indication'.

Novo Nordisk did not agree that the heading 'Do more than lower blood glucose' was misleading and inconsistent with the SPC and that the prominence of this headline misled readers about the product's licensed indication and in this regard did not encourage the rational use of liraglutide. The heading was a 'call to action', urging physicians managing type 2 diabetes to look beyond blood glucose and consider some of the widely accepted additional underlying pathologies. Further, this was approved by the MHRA, subject to inclusion of the indication in a prominent position. The indication for Victoza for the treatment of type 2 diabetes, which was taken verbatim from the SPC, was clear on the advertisement as per the MHRA's requirements.

The MHRA was happy with the box. It had commented about the draft lay out and suggested that references to other actions such as blood pressure effects were clearly separated from and subsidiary to the main indication so as not to suggest a wider indication than the SPC which Novo Nordisk did and which the MHRA approved.

Novo Nordisk disagreed that the wording, design and layout invited readers to make additional comparisons. It simply stated the clinically significant benefits beyond HbA1c control which was consistent with the SPC.

Novo Nordisk did not agree that the reference to reductions in weight and systolic blood pressure without the inclusion of the baseline parameters misled by omission. These claims simply highlighted the clinically important additional benefits of Victoza and could be substantiated by the cited randomized controlled trials (Marre *et al* 2009, Nauck *et al* 2009, Russell-Jones *et al* 2009) and Section 5.1 of the SPC.

The approval by EMEA was for all sulphonylureas even though the study was conducted with glimepiride, one of the most commonly prescribed sulphonylureas in Europe.

Novo Nordisk did not agree that the mention of the clinically and statistically relevant benefits of weight and systolic blood pressure went beyond what was supported by the SPC. There was clear reference to the clinical data that supported the clinically and statistically relevant changes for weight and systolic blood pressure. Throughout the LEAD studies the benefits of HbA1c, weight and systolic blood pressure had been seen for both Victoza 1.2mg and 1.8mg. The third dose of 0.6mg which formed a separate arm in some of the LEAD trials was only a starting (titration) dose and its benefits were not recorded as part of the SPC. No mention of dosing was contained within the advertisement so the assumption that the reader would make such a conclusion was unsubstantiated.

Novo Nordisk did not agree that the visual was inconsistent with the SPC and implied that Victoza could cure type 2 diabetes. The advertisement did not expressly or by implication convey that Victoza represented a cure for diabetes, or that it could delay disease progression.

The visual symbolized the apparent surface problem caused by type 2 diabetes - high blood glucose. It encouraged physicians to do more than treat the most obvious symptom (hyperglycaemia) but take a more holistic approach to treatment, including the additional benefits, which were contained within the SPC, that considering weight gain, blood pressure, and beta-cell function when treating patients with type 2 diabetes, inline with the recommendations of a number of diabetes associations, including EASD, IDF and American Diabetes Association (ADA). There was no mention in the advertisement that Victoza would normalize these parameters in all patients. That said, these additional product benefits were important treatment considerations that were supported by the SPC.

Further, the advertisement with the visual was approved by the MHRA.

Novo Nordisk did not agree that this advertisement breached the clauses of the Code cited by Lilly.

**PANEL RULING**

The Panel considered that the heading 'Do more than lower blood glucose' would encourage Victoza to be prescribed because of its effects beyond that of glycaemic control. In that regard the benefits of therapy had not been separated from or placed subsidiary to the main indication. A wider indication was implied. The reason to use Victoza, ie to reduce HbA1c, was the third piece of information on the page after the heading and the subheading which stated that 'Once-daily Victoza … impacts on multiple factors associated with type 2 diabetes …'. In the boxed text equal emphasis was given to 'Reductions in HbA1c' as to reductions in weight, systolic blood pressure and improvements in beta-cell function.

There was a difference between promoting a product for a licensed indication and promoting the benefits of using that product albeit that some of the benefits were specifically mentioned in the SPC. The Panel further noted that although the licensed indication for Victoza was for the treatment of type 2 diabetes in combination with metformin and/or a sulphonylurea or with metformin and a thiazolidinedione. The data regarding the benefits of therapy, however, was from studies using only glimepiride as the sulphonylurea and rosiglitazone as the thiazolidinedione. The Panel considered that the secondary effects on weight, systolic blood pressure and beta-cell function had not been placed sufficiently within the context of the primary reason for prescribing Victoza ie glycaemic control or within the limit of the data. This was inconsistent with the SPC and a breach of Clause 3.2 was ruled. This ruling was appealed.

The Panel did not consider that the advertisement invited a comparison with other antidiabetic medicines. The advertisement mentioned other oral antidiabetic medicines but there were no comparisons. It suggested that Victoza offered more than lowering of blood glucose but this was not necessarily unacceptable or disparaging. No breach of Clauses 7.3 and 8.1 was ruled.

The Panel noted its comments previously about weight changes in point A above (particularly in point A1). The weight changes were mean values and had not been quantified or qualified in the advertisement now at issue. The claim 'Reductions in weight' implied that this would be observed with both doses of Victoza (1.2mg and 1.8mg) in every licensed combination, was clinically and statistically significant and applicable to all patients. The claim was referenced to Nauck *et al* 2009 (LEAD 2), Russell-Jones *et al* 2008 (LEAD 5) and the SPC.

Nauck *et al* (LEAD 2) stated that weight loss was dose dependent in the liraglutide treatment groups; 2.6 ± 0.2kg and 2.8 ± 0.2kg for 1.2 and 1.8mg liraglutide combination groups respectively which was significantly different ($p<0.0001$) from the weight gain in the glimepiride group (1.0 ± 0.2kg). The weight loss in the 1.2mg and 1.8mg liraglutide combination groups was also statistically significantly greater ($p\leq0.01$) than the weight loss in the placebo group (1.5 ± 0.3kg). There was no mention of the percentage of patients which lost weight.

Russell-Jones (LEAD 5) stated that the mean weight loss, 1.8kg (SEM 0.33) in the 1.8mg liraglutide combination group (metformin plus glimepiride) was statistically significantly superior to the reduction in the placebo group (metformin plus glimepiride) 0.42kg (SEM 0.39) ($p=0.0001$). Weight increased by 1.6kg in the insulin glargine group.

The Panel did not accept that such weight loss data was needed for 0.6mg liraglutide to support the claim 'Reductions in weight'; the 0.6mg liraglutide dose was clearly a starting dose.

The Panel considered that the claim 'Reductions in weight' was too simplistic given the data. Although weight loss would benefit type 2 diabetics, the amount lost was small. Nonetheless some weight loss, however modest, was preferable compared with the weight gain associated with some other antidiabetic treatments. The SPC recorded weight gain data for Victoza 1.2mg plus glimepiride. It was important for health professionals to fully understand the magnitude of weight loss with Victoza and also that not every patient would lose weight. This was not possible from the claim at issue. The Panel considered that the claim was misleading, ambiguous and exaggerated; it could not be substantiated for each Victoza dose (1.2mg or 1.8mg) or licensed combination. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled. These rulings were appealed.

The claim 'Reductions in systolic blood pressure' was referenced to Marre *et al* (LEAD 1) 2009, Nauck *et al* (LEAD 2) and the SPC. The Panel noted its comments previously about reductions in systolic blood pressure (Point A). Marre *et al* (LEAD 1) stated that although decrease in blood pressure occurred with Victoza 1.2mg and 1.8mg combined with glimepiride (2.6 - 2.8mmHg) these were not significantly different from placebo or rosiglitazone. Nauck *et al* (LEAD 2) reported significant reductions in systolic blood pressure 2 - 3mmHg for 1.2mg and 1.8mg Victoza plus metformin compared with the increase observed with the glimepiride plus metformin group. The Victoza SPC stated that compared to active comparator the decrease in systolic blood pressure was 1.9 to 4.5mmHg.

The blood pressure changes had not been quantified in the advertisement. The claim 'Reductions in systolic blood pressure' implied that this applied to every licensed combination, was clinically and statistically significant. The SPC only referred to reductions in systolic blood pressure vs active comparator some of the results had not been statistically significantly different to placebo. It was important that health professionals fully understood the effects on blood pressure. This was not possible from the claim at issue. The Panel ruled that the unqualified and unquantified claim was misleading, ambiguous and exaggerated and could not be substantiated. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled. These rulings were appealed.

The Panel did not consider that the lollipop tree visual implied that Victoza could uproot type 2 diabetes and eliminate the illness. In the Panel's view it illustrated that there were a number of factors linked to type 2 diabetes. The Panel did not consider the visual was, in itself, inconsistent with the SPC as alleged. No breach of Clauses 3.2, 7.2, 7.4 and 7.8 was ruled.

The Panel considered that high standards had not been maintained and a breach of Clause 9.1 was ruled. This ruling was appealed. The Panel did not consider the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use.

**APPEAL BY NOVO NORDISK**

Novo Nordisk noted that the Panel considered that the advertisement implied a wider use for Victoza than the actual licensed indications, by alleging that the additional benefits had not been separated from or placed subsidiary to the licensed indication.

Novo Nordisk submitted that the advertisement did separate the main indication from the wider benefits. The effect of the licensed indication (HbA1c improvement) was clearly separated from the other benefits, which were listed under the subtitle of 'Additional benefits' and not in bold font. Furthermore, the licensed indication was also clearly set out directly under the highlighted box. It was inappropriate and unjust for the Panel to rule a breach of Clause 3.2 of the Code when the same item was approved by the MHRA as being in compliance with Regulations 3A(1) of the Advertising Regulations and Paragraph 4.3 of the Blue Guide. In addition, during the pre-vetting process, the MHRA provided clear direction in its letter of 20 May, 2009 about what to place on the sales aid (which had the same layout as the advertisement in issue) in order to prevent the implication of a wider indication. 'The product is indicated for diabetes for glycaemic control. You should ensure that the references to other actions such as BP effects are clearly separated from and subsidiary to the main indication so as not to suggest a wider indication than in the SPC'.

In response to this letter, Novo Nordisk created the current layout of several materials, including the advertisement at issue, in particular including the features described above, to ensure the additional benefits were separated from and subsidiary to the main indication. A revised version of the layout in this form was sent back to the MHRA which did not object to the layout (MHRA letter, 5 June 2009).

Novo Nordisk therefore denied that the advertisement was in breach of Clause 3.2 of the Code.

Novo Nordisk noted that the Panel considered that the claim 'Reductions in weight' was misleading, ambiguous and exaggerated and that it could not be substantiated for each Victoza dose (1.2mg or 1.8mg) or licensed combination. The Panel further stated that the amount of the weight loss was small and highlighted the weight gain data with liraglutide 1.2mg in combination with glimepiride. Furthermore, the Panel contended that health professionals needed to know the amount of weight loss in order to fully understand this benefit and that it should have been specified that not every patient would lose weight.

Novo Nordisk submitted that with respect to the charge that the claim was misleading, unsubstantiated and exaggerated, it reiterated its comments made in this regard in A1 above. As highlighted the only subpopulation which demonstrated clinically non-significant (0.23kg) weight gain in the LEAD programme was the 1.2mg Victoza group (in combination with glimepiride) from Marre *et al* (LEAD 1). All other patients in the phase 3a programme regardless of whether they were randomized to 1.2mg or 1.8mg Victoza (in combination with metformin, metformin and glimepiride or metformin and rosiglitazone) lost weight of between 1.0 and 2.8kg on average.

Novo Nordisk noted the Panel's comment that the amount of weight loss was small, but submitted that whilst numerically it might have been small, it was still a significant benefit. Furthermore, health professionals acknowledged the unfavourable impact of weight gain or the favourable effect of weight loss on cardiovascular risk which was particularly important in type 2 diabetics. Lean *et al*, (1990), highlighted the importance of weight loss (even a minimum of 1kg) in type 2 diabetes which was associated with improved survival. More generally, even 1kg of weight gain in adulthood might increase the risk of coronary heart disease by 3.1 – 5.7% in the general population depending on gender (Anderson *et al*, 2001) and the same paper also described the importance of 1kg weight loss from the perspective of different cardiovascular risk factors.

Additionally, Novo Nordisk submitted that an expectation that a medicine would work in every patient in order to make a claim relating to its effect was clinically unfounded, as discussed in A1 above. Health professionals had realistic expectations in the clinical setting and they therefore interpreted such claims realistically – ie that the claimed effect was shown in a statistically significant number of patients, but there was no guarantee that it would occur in all.

Whilst Clauses 7.2 and 7.4 of the Code and Regulations 3A(2) and (3) of the Advertising Regulations/Paragraph 4.3 of the Blue Guide were not entirely equivalent, Novo Nordisk noted that pre-vetting against such requirements took place.

On the basis of the above, Novo Nordisk disagreed with the Panel that the weight claim in the advertisement was in breach of Clauses 7.2, 7.4 and 7.10 of the Code.

Novo Nordisk noted that the Panel considered that the claim 'Reductions in systolic blood pressure' was also misleading, ambiguous, exaggerated and not capable of substantiation. Section 5.1 of the SPC stated that Victoza decreased the systolic blood pressure on average by 2.3 to 6.7mmHg from baseline. This magnitude of systolic blood pressure drop was clearly clinically significant. According to the Prospective Studies Collaboration (2002), which analyzed the relevance of age-specific blood pressure to cause-specific mortality in 61 prospective observational studies (12.7 million person-years), even 2mmHg lower usual systolic blood pressure would involve about 10% lower stroke mortality and 7% lower ischaemic heart disease mortality. The systolic blood pressure reduction was a consistent finding throughout the LEAD trials. Nauck *et al* (LEAD 2) and Russell-Jones (LEAD 5) the reduction was statistically significantly greater than with the active comparator, whilst in Zinman *et al* (LEAD 4) it was statistically significantly larger than with the placebo (in this trial there was no active comparator tested). The only trial where the reduction did not reach the level of statistical significance (vs active comparator) was Marre *et al* (LEAD 1), although the magnitude of the blood pressure drop (2.6-2.8mmHg) seemed to be clinically significant on the basis of the Prospective Studies Collaboration (2002).

Thus Novo Nordisk submitted that the systolic blood pressure reduction claim was capable of substantiation, it was neither misleading nor ambiguous and was not exaggerated. Whilst Clauses 7.2 and 7.4 of the Code and Regulations 3A(2) and (3) of the Advertising Regulations/ Paragraph 4.3 of the Blue Guide were not entirely equivalent, Novo Nordisk noted that pre-vetting against such requirements took place.

Novo Nordisk therefore did not agree with the rulings by the Panel that this was in breach of Clauses 7.2, 7.4 and 7.10 of the Code.

On the basis of the above appeals Novo Nordisk submitted that the advertisement complied with the spirit of the Code and did not breach any of the above cited clauses by the Panel. It could not therefore be said that high standards had not been maintained and Novo Nordisk therefore also disagreed with the Panel's ruling of a breach of Clause 9.1.

**COMMENTS FROM LILLY**

Lilly noted that in a letter of 20 May 2009 the MHRA had asked Novo Nordisk to 'justify the claim "Get to the roots of type 2 diabetes". This could imply that the treatment will cure the disease' and 2 which stated 'The product is indicated for diabetes for glycaemic control. You should ensure that the references to other actions such as BP effects are clearly separated from and subsidiary to the main indication so as not to suggest a wider indication than in the SPC', The MHRA's question appeared to reflect the very concerns outlined by Lilly in its complaint.

**APPEAL BOARD RULING**

The Appeal Board noted that the advertisement stated 'Once-daily Victoza, in combination with metformin and/or a sulphonylurea, impacts on multiple findings associated with type 2 diabetes providing from baseline' below which were four bullet points; the first was 'Reductions in HbA1c'

which referred to the indication for Victoza. The next three bullet points were then separated from the first by a space followed by the words 'And in addition:' The next three bullet points were: 'Reductions in weight'; 'Reductions in systolic blood pressure' and 'Improvements in beta-cell function'. The Appeal Board considered that the separation of the indication for Victoza ie, lowering blood glucose, from its additional benefits was sufficient. The Appeal Board considered that the advertisement was not inconsistent with the Victoza SPC and ruled no breach of Clause 3.2. The appeal on this point was successful.

The Appeal Board noted that the Victoza SPC stated that weight loss ranged 'from 1.0kg to 2.8kg'. The Appeal Board considered that the claim 'Reductions in weight' was not inconsistent with the available data and the Victoza SPC. Health professionals would not expect every patient to lose weight with Victoza. The Appeal Board did not consider that the claim was misleading or incapable of substantiation or exaggerated. The Appeal Board ruled no breach of Clauses 7.2, 7.4 and 7.10. The appeal on this point was successful.

The Appeal Board noted the claim 'Reductions in systolic blood pressure' was referenced to Marre *et al* (LEAD 1), Nauck *et al* (LEAD 2) and the SPC. Marre *et al* (LEAD 1) stated that although blood pressure decreased with Victoza 1.2mg and 1.8mg combined with glimepiride (2.6 – 2.8mmHg) the change was not significantly different from that observed with placebo or rosiglitazone. Nauck *et al* (LEAD 2) reported significant reductions in systolic blood pressure (2 – 3mmHg) for 1.2mg and 1.8mg Victoza plus metformin compared with the increase observed with the glimepiride plus metformin group. The Victoza SPC stated that over the duration of the studies Victoza decreased systolic blood pressure on average 2.3 to 6.7mmHg from baseline and compared to active comparator the decrease in systolic blood pressure was 1.9 to 4.5mmHg. The Appeal Board noted that even a small reduction in systolic blood pressure was considered to be clinically relevant. The Appeal Board considered that the claim 'Reductions in systolic blood pressure' was not inconsistent with the data and the Victoza SPC. The Appeal Board did not consider that the claim was misleading, exaggerated or incapable of substantiation. The Appeal Board ruled no breach of Clauses 7.2, 7.4 and 7.10. The appeal on this point was successful.

The Appeal Board noted its rulings above and considered that Novo Nordisk had not failed to maintain high standards. The Appeal Board ruled no breach of Clause 9.1. The appeal on this point was successful.

**2 Reprint folders (UK/LR/0409/0085 and UK/LR/0609/0202)**

The folders at issue were similar to each other; the front cover of each included the same claims and illustration as in the advertisement at issue in Point B1 above. One folder (UK/LR/0609/0202) additionally included the claim 'SMC [Scottish Medicines Consortium] Pending' on the front cover in a yellow box. The back cover included a list of references and the prescribing information.

The folders provided by Novo Nordisk were empty and there was no mention as to what was provided in the folders.

**COMPLAINT**

Lilly stated that its comments about the advertisement in Point B1 above applied to the front covers of the folders.

Lilly further alleged that the highlighted and prominent statement 'SMC Pending' was misleading. In itself the wording was, at best, meaningless however, Novo Nordisk's intent behind this was clear given the promotional context in which it was introduced. 'Pending' was synonymous with imminent, prospective, impending and had a very particular meaning in regulatory parlance as would be employed by organisations such as the SMC. In this regard, this statement clearly inferred that Victoza had been accepted for use within NHS Scotland pending formal ratification by the SMC. The SMC had stated that its decision on the acceptability of Victoza would be published on 7 December 2009. The claim was clearly misleading and undermined prescriber confidence in the pharmaceutical industry and patient safety. Lilly alleged a breach of Clauses 2, 7.2, 7.4, 7.10 and 9.6.

**RESPONSE**

Novo Nordisk referred to its response to Point B1 above and also to the correspondence from the MHRA of 3 June 2009 (a copy of which was provided), which provided approval of one of the folders (UK/LR/0409/0085).

Novo Nordisk disagreed that the statement 'SMC Pending' implied that would be approved by the SMC. The SMC was currently evaluating Victoza, and would publish its decision would on 7 December 2009. 'SMC pending' reflected the fact that Victoza was currently being reviewed by the SMC.

Novo Nordisk disagreed that this material was in breach as alleged by Lilly.

**PANEL RULING**

The Panel considered that its rulings at Point B1 above applied here. These rulings were appealed.

With regard to the phrase 'SMC Pending' the Panel noted that 'pending' could be variously defined as, *inter alia*, 'while waiting for', 'not yet decided, confirmed or finished' and 'imminent'. The Panel considered that the claim 'SMC Pending' strongly

implied that SMC approval was a formality or a matter of time rather than reflecting that Victoza was going through the SMC process. The Panel considered the claim was ambiguous and thus misleading. A breach of Clause 7.2 of the Code was ruled. The Panel considered that the fact that the SMC was actively considering the product was sufficient with regard to the requirement to provide substantiation and thus no breach of Clause 7.4 was ruled. The claim did not exaggerate the position nor was it a claim for a special merit. No breach of Clause 7.10 was ruled.

The Panel ruled no breach of Clause 9.6. Novo Nordisk had not reproduced an official document without permission.

The Panel did not consider that the use of the phrase 'SMC Pending' warranted a ruling of Clause 2 which was a sign of particular censure and reserved for such use.

**APPEAL BY NOVO NORDISK**

Novo Nordisk submitted that since the Panel considered that its rulings at Point B1 applied here, it repeated its comments and position set out in B1.

Novo Nordisk noted that in light of the breach accepted in respect of the phrase 'SMC Pending', reprint folder UK/LR/0609/0202 had been withdrawn.

**COMMENTS BY LILLY**

There were no comments from Lilly.

**APPEAL BOARD RULING**

The Appeal Board noted it comments and rulings in Point B1 above regarding the advertisement which it considered also applied here.

**3 Leavepieces 'Do more than lower blood glucose' (UK/LR/0409/0079 and UK/LR/0609/0192)**

The two leavepieces were similar to each other; page 1 of each was the same as the front cover of the reprint folders at issue in Point B2 above ie one had 'SMC Pending' (UK/LR/0609/0192) and one did not (UK/LR/0409/0079).

Page 2 of the leavepiece was headed 'Victoza + metformin effectively reduced HbA1c' and showed data adapted from Nauck *et al* (LEAD 2).

Page 3 was headed 'In addition: Victoza + metformin help patients achieve early weight loss' and was referenced to Nauck *et al* (LEAD 2) and Novo Nordisk data on file.

The subheading on Page 3 'Weight loss was seen at 2 weeks and totalled 2.6kg at 26 weeks compared with metformin + glimepiride (1kg weight gain at 26 weeks)' was referenced to Nauck *et al* (LEAD 2) and Novo Nordisk data on file. A graph of the data appeared beneath the subheading.

**COMPLAINT**

Lilly repeated its comments at Point B1 regarding page 1 of the leavepieces.

The heading on page 2 'Victoza + metformin effectively reduce HbA1c' was followed by 'Victoza + metformin provide significant reductions in HbA1c compared with metformin alone – with a low risk of hypoglycaemia' and referenced to Nauck *et al* LEAD 2. This was followed by a bar chart which compared the mean change from baseline HbA1c (8.4%) in patients previously treated with oral antidiabetic monotherapy at 26 weeks. The bar chart depicted a reduction from baseline of 1.25% for Victoza 1.2mg in combination with metformin 2000mg, a reduction of 0.38% for metformin 2000mg and a reduction of 1.15% for glimepiride 4mg combined with metformin 2000mg. Statistical significance of $p<0.0001$ vs metformin 2000mg was assigned with respect to the mean reduction from baseline in HbA1c of 1.25% for Victoza 1.2mg in combination with metformin 2000mg.

Lilly alleged that the claimed reduction in HbA1c by 1.25% was only true for the subgroup of patients in Nauck *et al* (LEAD 2) that were previously treated with monotherapy. This subgroup comprised only 35% of the total study population. For all patients treated with Victoza, however, this statement was incorrect and misleading. Table 2 in Section 5.1 of the Victoza SPC, indicated that the mean reduction in baseline in HbA1c for liraglutide 1.2mg in combination with metformin 2000mg was 0.97% and not 1.25%. The 0.97% reduction was also consistent with the results reported for the total population in Nauck *et al* (LEAD 2). The claim in question was therefore misleading, incorrect and inconsistent with the SPC. The chart also misled by omission and association with reference to the results reported for glimepiride 4mg combined with metformin 2000mg; there was no indication that the comparison with the Victoza 1.2mg arm was not statistically significant, albeit this was pre-specified in the statistical analysis plan for the study.

The layout of the chart invited a direct comparison of the relative efficacy of Victoza, metformin and glimepiride with regard to reductions in HbA1c from baseline and misleadingly indicated a superior benefit associated with Victoza 1.2mg compared with glimepiride 4mg. Nauck *et al* (LEAD 2) clearly stated that no such inference could be drawn given that there was no difference in the HbA1c reduction between Victoza and glimepiride. The reader was also misled by omission of the fact that the HbA1c reduction in two-thirds of the patients in Nauck *et al* (LEAD 2) was -0.68% for Victoza 1.2 mg and 0.78% for glimepiride 4mg. The reader was also misled with respect to the selective use of data from Nauck *et al* (LEAD 2). Omission of the comparative results for Victoza 1.8mg misled the reader regarding the

comparative efficacy of this particular dose vs Victoza 1.2mg and glimepiride 4mg. Given that the mean change from baseline in HbA1c for Victoza 1.8mg in combination with metformin 2000mg was 1%, Lilly suspected this was a convenient and commercially driven omission designed to avoid the obvious conclusion that the higher dose of Victoza was no more efficacious than Victoza or glimepiride 4mg. Importantly, the claims were not substantiated by Nauck *et al* (LEAD 2) given that neither this study nor any other published reported pre-specified a direct comparison of Victoza vs metformin monotherapy as was stated on this page. Thus the claims 'Victoza + metformin provide significant reductions in HbA1c compared with metformin alone ...' and 'p<0.0001 vs. metformin' were factually incorrect and misleading. The comparison was not with metformin monotherapy but with a placebo as clearly highlighted in the Victoza SPC and Nauck *et al* (LEAD 2).

The first bullet point beneath the chart on page 2 stated in emboldened font that 'Some patients experienced even greater reductions in HbA1c – patients with baseline HbA1c levels above 9.5% experienced a 2.74% reduction in HbA1c with Victoza 1.2mg in combination with metformin'. The claim was referenced to Nauck and Marre (2009).

Lilly alleged that this claim was misleading as it relied on cherry-picked and incorrect data. Nauck and Marre, a post-hoc analysis of two phase III randomised control clinical trials, LEAD 1 and LEAD 2 was cited in support of the claim. The analysis, involving 386 subjects, included only the 1.8mg dosage of Victoza and not the 1.2mg dosage as was asserted. The claim was therefore not only factually inconsistent with the citation but it also did not represent the balance of evidence as represented by the five double blind, randomised controlled trials conducted in 3,978 patients to evaluate the effects of Victoza 1.2mg on glycaemic control. Indeed, the authors stated that the:

> 'Glycosylated haemoglobin reductions with liraglutide, placebo and the active comparator in the subset of patients previously on OAD [oral antidiabetic therapy] monotherapy were larger than previously published results observed in the total patient population, which included patients on previous OAD monotherapy and combination therapy. This may reflect the fact that patients in the current analysis had less advanced diabetes than the total OAD therapy populations examined in the earlier studies'.

Notwithstanding that this claim was not substantiated by the reference, the incredibly selective and unbalanced aspect of this claim was evidenced by the very small number of LEAD 2 subjects (n = 16) with particularly high baseline HbA1c previously on oral monotherapy upon which it relied for apparent substantiation. The authors stated that 'It is difficult to compare HbA1c reductions across unrelated trials because of differences in patient populations and protocols' thereby highlighting the significant limitations of the data in support of any such claim. In inter-company dialogue Novo Nordisk asserted that this claim was fully substantiated and not incorrect; notwithstanding this, Novo Nordisk had agreed to remove it from the leavepiece but did not confirm that this misleading leavepiece, as well as all other Victoza materials containing this claim, had been withdrawn from use with immediate effect, as per Lilly's request.

The next bullet points on page 2 of the leavepiece referred to hypoglycaemic events:

> 'Statistically, fewer minor hypoglycaemic events were observed with Victoza in combination with metformin compared with metformin in combination with glimepiride (p<0.001)' referenced to Nauck *et al* (LEAD 2).

and

> 'No major hypoglycaemic events were observed with Victoza in combination with metformin [referenced to Nauck *et al* (LEAD 2)]. In a separate study, no major hypoglycaemic events were observed with Victoza in combination with metformin and a thiazolidinedione (TZD) [referenced to Zinman *et al* 2009 (LEAD 4)]'.

Lilly alleged that the focus of the classification of hypoglycaemic events with respect to severity (ie minor and major events) and incidence (ie low risk, fewer, no events) was misleading and unbalanced as it implied that hypoglycaemia did not occur commonly and was of no clinical consequence to either patients or prescribers. The latter was also evidenced by the third bullet point which stated 'In a separate study, no major hypoglycaemic events were observed with Victoza in combination with metformin and a thiazolidinedione (TZD)'. This was inconsistent with the Victoza SPC which stated that hypoglycaemia was common and very common with respect to Victoza when combined with glimepiride, metformin and glimepiride and metformin and rosiglitazone; this was irresponsible and potentially compromised patient safety.

Lilly alleged that page 3 of the leavepiece further misled with regard to the licensed indication of Victoza by promoting it as an anti-obesity medicine. The heading 'In addition: Victoza + metformin help patients achieve early weight loss' referred to 'Victoza' which invited the reader to consider that the weight reduction was applicable to all doses of liraglutide. This impression was further emphasised in the sub-heading which emphasised the early reduction in 'weight loss seen at 2 weeks' compared to metformin and glimepiride 4mg. It was only in the graph which followed that specific reference, in very small font, was made to Victoza 1.2mg in combination with metformin. Given the prominence of the unqualified reference to 'Victoza' in the headline, the reader was misled to believe that the magnitude and timing of the weight reduction

reported in the graph was applicable to all doses of liraglutide when combined with metformin, glimepiride and rosiglitazone. Thus the weight reduction reported on this page for Victoza 1.2mg was selective, did not represent the balance of evidence and was inconsistent with the SPC which stated that 'Victoza in combination with metformin, metformin and glimepiride or metformin and rosiglitazone was associated with sustained weight reduction over the duration of studies in a range from 1.0kg to 2.8kg'.

The prominence given to discussion of the weight reduction was skewed and inconsistent with the primary efficacy endpoint of the cited study which was to assess the mean change from baseline in HbA1c at 26 weeks and not weight reduction, as implied. In the absence of p-values, reporting 'early' weight reduction after two weeks implied statistical significance to this observation; this was misleading and inconsistent with the statistical analysis plan.

In the absence of any indication of the baseline body weight and BMI, by which the implied clinical and statistical significance of the reductions referred to could be assessed, the claims about weight reduction misled readers by omission and exaggerated the results. Lilly noted that the Victoza SPC stated that 'Larger weight reduction was observed with increasing body mass index (BMI) at baseline'.

The improvements in HbA1c discussed on page 2 were appropriately contextualised with references to the severity and incidence of hypoglycaemia. However, given that the weight loss associated with liraglutide was attributed to delayed gastric emptying, it would have been equally appropriate to inform readers of the incidence of nausea, diarrhoea, vomiting, dyspepsia which variously occurred commonly or very commonly with liraglutide. This omission misled by omission and potentially compromised patient safety.

At the bottom of page 3 it was stated 'Weight loss with Victoza provides reductions in visceral fat' and 'Visceral fat was reduced by 13% to 16% in patients treated with Victoza vs. 8% in placebo-treated patients' reference to Jendle *et al* (2008). In the absence of percentages indicating the proportion of visceral fat at baseline, and the clarification that the comparison was relative to abdominal subcutaneous adipose tissue, as opposed to lean body tissue or total fat, the clinical significance and relevance of this observation was questionable and therefore misled the reader and exaggerated the facts. The visceral tissue was only assessed with reference to Nauck *et al* (LEAD 2) which looked at liraglutide in combination with metformin vs placebo or glimepiride 4mg. Thus the claim was misleading as it invited relevance of this observation to liraglutide when combined with other oral antidiabetics such as rosiglitazone.

Lilly stated that all of the concerns outlined above also related to item number UK/LR/0609/0192. With respect to the latter, the concerns outlined in point B2 were also relevant.

Lilly alleged that the leavepiece was in breach of Clauses 2, 3.2, 7.2, 7.3, 7.4, 7.8, 7.10, 8.1 and 9.1 of the Code.

**RESPONSE**

Novo Nordisk referred to its response to Point A2 above.

Novo Nordisk submitted that the leavepiece, focused, (as described in the headline), on once daily Victoza 1.2mg in combination with metformin. As referenced, this clinical situation was examined in Nauck *et al* (LEAD 2). The reduction in HbA1c in the subgroup of patients receiving prior oral therapy was clearly stated in Nauck *et al* (LEAD 2) with a detailed description of the effect according to previous treatment.

Nauck *et al* (LEAD 2) was included in this leavepiece as it was the only LEAD study that investigated the combination of Victoza and only metformin. The inclusion of this data, therefore, aligned this leavepiece with the published Nathan *et al* (2009) guidelines.

The claim regarding the reduction of HbA1c by 1.25% in patients receiving prior oral monotherapy reflected 'real-life' clinical prescribing, where patients would receive liraglutide as 'add-on' treatment to one oral antidiabetic medicine. This was consistent with the treatment sequence as recommended in the global guidelines, Nathan *et al*. Novo Nordisk, therefore, disputed that the statement was misleading, or factually incorrect. The asterisk presented in the -1.25% bar for liraglutide 1.2mg clearly indicated that this was $p<0.0001$ vs metformin. There was no significant difference to glimepiride and therefore, Novo Nordisk maintained that no further symbols were needed to denote this. Novo Nordisk did not believe that the absence of a symbol to denote non-significance was entirely appropriate and did not mislead by omission.

Furthermore, Novo Nordisk disputed that the layout of the graph indicated a superior benefit associated with 1.2mg liraglutide compared with glimepiride 4mg, for the reasons stated above.

As mentioned above, patients receiving previous monotherapy (one third) reflected real-life clinical prescribing in which liraglutide would be 'added on' to one oral antidiabetic medicine. The subgroup of patients (two thirds) receiving combination oral antidiabetic therapy prior to trial had one of two oral antidiabetics removed, which was then substituted with liraglutide. This scenario did not reflect real-life clinical prescribing and, therefore, was not relevant for discussion in this leavepiece. Novo Nordisk, therefore, disputed that the reader was misled by omission.

The standard Victoza treatment dose was 1.2mg;

some patients were expected to benefit from an increase in dose to 1.8mg. In this leavepiece, Novo Nordisk promoted the 1.2mg standard dose only, in accordance with the licensed indications. Novo Nordisk therefore disputed that this was convenient or commercially-driven omission as alleged.

Patients randomised to the placebo arm of Nauck *et al* (LEAD 2) received metformin monotherapy, therefore, the claim 'Victoza + metformin provide significant reductions in HbA1c compared with metformin alone' and 'p<0.0001 vs. metformin' were substantiated by Nauck *et al* (LEAD 2).

With regard to the claim '… patients with baseline HbA1c levels of above 9.5% experienced a 2.74% reduction in HbA1c with Victoza in combination with metformin', Novo Nordisk disputed that this was incorrect data as the claim was fully substantiated by the cited reference, Nauck and Marre 2009. However, Novo Nordisk had agreed to remove this statement in this UK leavepiece.

In response to the concern raised by Lilly with regard to the classification of hypoglycaemia events, the SPC stated:

'Most episodes of confirmed hypoglycaemia in clinical studies were minor. No episodes of major hypoglycaemia were observed in the study with Victoza used as monotherapy. **Major hypoglycaemia may occur** uncommonly and has primarily been observed when Victoza is combined with a sulphonylurea (0.02 events/subject year). **Very few episodes** (0.001 events/subject year) **were observed with administration of Victoza in combination with oral antidiabetics other than sulphonylureas**.' (emphasis added).

As such, the language used in this leavepiece with regard to hypoglycaemia was appropriate and consistent with the SPC. Novo Nordisk did not believe that the leavepiece implied that hypoglycaemic events were of no clinical consequence to patients or prescribers.

With regard to page 3 of the leavepiece Novo Nordisk stated that the allegation that it referred to only Victoza in this leavepiece was incorrect. The heading actually stated 'In addition: Victoza + metformin help patients achieve early weight loss' and was appropriately referenced to Nauck *et al* (LEAD 2). In this study, weight reduction was applicable to all doses of liraglutide in combination with metformin. Novo Nordisk believed the heading was substantiated and was clearly referenced.

Novo Nordisk was confused by the allegation that given the prominence of the unqualified reference to 'Victoza' in the heading, the reader was misled to believe that the magnitude and timing of the weight reduction reported in the graph was applicable to all doses of liraglutide when combined with metformin and glimepiride and rosiglitazone. As stated above, the heading on page 3 stated 'In addition: Victoza + metformin help patients achieve early weight loss' and was appropriately referenced to Nauck *et al* (LEAD 2) which confirmed that weight loss was associated with all doses of liraglutide when used in combination with metformin.

Novo Nordisk disputed that presenting weight reduction for the 1.2mg Victoza dose only was selective. The Victoza SPC suggested that the standard treatment dose was 1.2mg. As such, in this leavepiece, Novo Nordisk had promoted the 1.2mg dose, in accordance with the licensed indications.

If it were being selective in the dose presented, it could have used the data about the non-standard 1.8mg dose where a weight reduction of 2.8kg was shown, rather than the 2.6kg weight reduction presented. Novo Nordisk was unclear why Lilly alleged it was being selective, given the above and the fact that the data presented on weight reduction fell within the range stated in the SPC.

Novo Nordisk did not agree that the prominence of the weight reduction results on page 3 skewed the endpoint of the study. The inclusion of data on weight reduction appeared on page 3 following discussion regarding the primary efficacy endpoint of this study, namely the reduction in HbA1c on page 2.

Novo Nordisk had not included any mention of statistical significance in relation to the claim that early weight loss was seen. Therefore, Novo Nordisk disputed that the absence of a statement claiming statistical significance could actually imply that statistical significance existed.

With regard to the absence of any indication of the baseline body weight and BMI, Novo Nordisk noted that Nauck *et al* (LEAD 2) did not involve a specific patient population with type 2 diabetes but recruited typical type 2 diabetics. Thus Novo Nordisk believed that any clinician that cared for such people could easily evaluate and interpret the clinical importance of the magnitude of the weight loss indicated on the graph without specifying the baseline values of the above parameters.

Novo Nordisk submitted that it would not be appropriate in the leavepiece to go into detail regarding adverse events associated with delayed gastric emptying, since the mechanisms of weight loss were not referred to, and were beyond the scope of the leavepiece. Novo Nordisk further disputed that this omission potentially compromised patient safety, particularly given that the prescribing information which set out the warnings and precautions for use was included.

Novo Nordisk did not agree that the claim stated at the bottom of page 3 'Weight loss with Victoza provides reductions in visceral fat' suggested that this observation was relevant to combinations with other oral antidiabetic medicines rather than only when Victoza was combined with metformin, given the bold large font heading at the top of this page clearly stated the observation was when Victoza

was used with metformin.

Novo Nordisk did not believe that the absence of percentages indicating the proportion of visceral fat at baseline in study subjects was misleading. The claim simply emphasized the clinically important change in visceral fat and put it in context with the observed change with placebo. In this regard the baseline percentage of visceral fat would not add any significant additional information.

The reduction in visceral fat, regardless of whether it was compared with abdominal subcutaneous fat, lean body tissue or total fat was of clinical significance to patients and prescribers and therefore Novo Nordisk believed that its inclusion was entirely justified.

As Novo Nordisk stated in inter-company dialogue, the statement 'Some patients experienced even greater reduction in HbA1c – patients with baseline HbA1c levels of 9.5% experienced a 2.74% reduction in HbA1c with Victoza 1.2mg in combination with metformin' had been removed from the promotional materials. During inter-company dialogue the original pieces (refs UK/LR/0409/0079 and UK/LR/0609/0192) were no longer in use (both pieces were formally withdrawn on 9 September 2008 sic) and had now been replaced with new materials (UK/LR/0809/0380 and UK/LR/0809/0381). Copies of the original and the new pieces were provided.

Given the above, Novo Nordisk denied that the material was in breach as alleged.

**PANEL RULING**

The Panel considered that its rulings at Point B1 above applied here. These rulings were appealed. With regard to the phrase 'SMC Pending' the Panel considered its ruling at point B2 above applied here.

Turning to page 2 of the leavepiece the Panel noted that Nauck *et al* (LEAD 2) assessed the efficacy and safety of adding Victoza to metformin compared with the addition of placebo or glimepiride to metformin in subjects previously treated with oral antidiabetic (OAD) therapy. The majority of patients were treated with two OADs before the study. The authors stated that mean HbA1c values for the overall population decreased by 1.0 ± 0.1% for both the 1.2mg and 1.8mg liraglutide groups and the glimepiride group. The bar chart at issue, however, was for the subgroup of patients whose previous OAD therapy was monotherapy. The small print next to the bar chart in the leavepiece stated that it related to a subgroup analysis. The page heading and sub-heading, however, did not refer to previous OAD monotherapy. The overall result and the result for those who had combination OAD therapy prior to the study (these reductions being 0.68% for liraglutide 1.2mg, 0.71% for liraglutide 1.8mg and 0.78% for glimepiride 4mg) showed less of a difference between liraglutide and glimepiride than the result for those who had OAD monotherapy as previous treatment which was the only data in the bar chart in the leavepiece.

The Panel did not consider that the claim in question 'Victoza + metformin provide significant reductions in HbA1c compared with metformin alone …' was misleading in that Nauck *et al* (LEAD 2) stated that HbA1c values were significantly reduced in all liraglutide groups v placebo ($p<0001$) with mean decreases of 1.0% for 1.2mg and 1.8mg of liraglutide and glimepiride and an increase of 0.1% for placebo. No breach of Clause 7.2 was ruled. The Panel noted that Nauck *et al* (LEAD 2) compared various doses of liraglutide plus metformin with placebo plus metformin or metformin plus glimepiride. The explanation '$p<0.0001$ versus metformin' was confusing in that every combination included metformin. A breach of Clause 7.2 was ruled in this regard.

The Panel considered the chart was misleading in that only the results for patients pretreated with OAD monotherapy were shown. Thus the Panel ruled a breach of Clauses 7.3, 7.8 and 7.10 of the Code. The Panel considered that the asterisk by the liraglutide data would be assumed to indicate a statistically significant difference. No explanation was given. The lack of the asterisk by the glimepiride/metformin data could be read as implying there was a difference between this and Victoza 1.2mg plus metformin with regard to HbA1c changes from baseline and when considering the overall results rather than the results for patients previously treated with monotherapy; this was not so. The Panel could not find any statistical details regarding this in Nauck *et al* (LEAD 2) but there was a general statement that the HbA1c profiles of subjects stratified by prestudy therapy, monotherapy or combination therapy were similar in appearance to those of the overall population and that 'the baseline and end of study mean [HbA1c] values in the monotherapy group were slightly less than those in the combination therapy group, and the resulting change-from-baseline decreases appeared to be slightly greater in the monotherapy group than in the combination therapy group'. In that regard the Panel considered that the data had been cherry-picked to show the results which demonstrated the largest positive difference for Victoza. A further breach of Clause 7.3 and 7.8 of the Code was ruled. The impression could not be substantiated and a breach of Clause 7.4 was ruled. The Panel considered that the positioning and presentation of the claim '$p<0.0001$ versus metformin' above the glimepiride reinforced the misleading impression of a statistically significant difference between the Victoza + metformin and the glimepiride + metformin data. This was misleading and a breach of Clause 7.2 was ruled.

The presentation of the data was inconsistent with the SPC and a breach of Clause 3.2 was ruled. This ruling was appealed.

The Panel noted that Novo Nordisk had agreed to remove the claim 'Some patients experienced even greater reductions in HbA1c – patients with baseline

HbA1c levels above 9.5% experienced a 2.74 reduction in HbA1c with Victoza 1.2mg in combination with metformin' from the leavepiece. The Panel was unsure whether the claim appeared in any other promotional material and this point had not been addressed in Novo Nordisk's response, either to Lilly or to the Authority. Nonetheless, it appeared that inter-company dialogue had been successful and thus the Director decided that the Panel should not consider the allegation about this claim.

The Panel noted that the SPC stated that hypoglycaemia was common and very common when Victoza was used in combination with a sulphonylurea. Major hypoglycaemia had primarily been observed when combined with a sulphonylurea. The SPC listed hypoglycaemia as common with liraglutide plus metformin plus rosiglitazone and liraglutide plus glimepiride. Hypoglycaemia was very common with liraglutide plus metformin and glimepiride.

The Panel noted that the claim 'Statistically, fewer minor hypoglycaemic events were observed with Victoza in combination with metformin compared to metformin in combination with glimepiride ($p<0.001$), referenced to Nauck *et al*, (LEAD 2) reflected the evidence from that trial and also the information in the SPC where no frequency of hypoglycaemia was stated for liraglutide with metformin. In that regard the Panel did not consider that the claim was misleading. No breach of Clause 7.2 was ruled. However, in the Panel's view, the claim 'In a separate study, no major hypoglycaemic events were observed with Victoza in combination with metformin and a thiazolidinedione (TZD)' sought to minimize a clinician's concerns regarding the occurrence of hypoglycaemia in this treatment group. The SPC listed hypoglycaemia as common in patients being so treated. Omission of this data, given the inclusion of data about major hypoglycaemia, was misleading. A breach of Clause 7.2 was ruled.

The Panel noted that page 3 presented the weight loss data for Victoza 1.2mg in combination with metformin although, as before, the heading and subheading did not make it clear that the results were for one dose of Victoza only. The Panel noted that the weight loss shown for Victoza plus metformin (2.6kg) was within the range stated in the general comment in the SPC that sustained weight reduction over the duration of studies ranged between 1.0kg to 2.8kg (both 1.2mg and 1.8mg Victoza doses). The data was an accurate reflection of Nauck *et al* (LEAD 2) and it clearly related to Victoza combined with metformin. No breach of Clauses 7.2 and 7.3 was ruled.

The Panel did not consider the presentation of the weight loss data was skewed and inconsistent with the fact that the primary efficacy endpoint of the study was to assess changes in HbA1c. The Panel noted its comments in this regard in Point B1 above.

The Panel did not consider that the reference to early weight loss and the absence of p values in this regard implied a statistically significant difference as alleged. The Panel ruled no breach of Clause 7.2 of the Code.

The Panel considered that although it would have been helpful to have an indication of baseline body weight the absence of this data was not necessarily misleading. No breach of Clause 7.2 was ruled.

The Panel did not consider that the omission of data regarding the incidence of nausea, diarrhoea, vomiting, dyspepsia from this page was misleading as alleged. No breach of Clauses 7.2 and 7.10 was ruled.

The Panel noted that Jendle *et al* was entitled 'The reduction in bodyweight with liraglutide, a once-daily human GLP-1 analogue for type 2 diabetes, primarily comes from fat tissue and the fat tissue lost is predominately visceral fat'. The data was preplanned substudies of data from LEAD 2 and LEAD 3. The differences between treatment groups for the changes from baseline were statistically significant for liraglutide 1.2mg and 1.8mg each vs glimepiride for visceral adipose tissue ($p<0.05$).

The Panel did not consider that the visceral fat data in the leavepiece in the absence of clarification that the comparison was relative to abdominal subcutaneous adipose tissue was in itself misleading or that the omission of details of baseline values was misleading or exaggerated the facts as alleged. No breach of Clauses 7.2 and 7.10 was ruled.

The Jendle *et al* data was relevant to the page in the leavepiece which referred to a glimepiride comparison. There was no mention of rosiglitazone. Thus the Panel did not consider that readers would infer that the visceral fat data was relevant in that regard and the Panel did not consider the leavepiece was disparaging. Lilly had not made a detailed allegation in this regard. No breach of Clause 8.1 was ruled.

The Panel considered that overall the leavepieces failed to maintain high standards and a breach of Clause 9.1 was ruled. With regard to Clause 2 the Panel did not consider that the leavepieces warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use.

**APPEAL BY NOVO NORDISK**

Novo Nordisk submitted that since the Panel considered that its rulings at Point B1 applied here, it repeated its position set out in B1.

In addition, as to the specific rulings related to these pieces, the Panel considered that the explanation of statistical significance that appeared in the graph on page 2 of the leavepieces was misleading. Novo Nordisk accepted this ruling and pointed out that

these materials had been amended recently to provide clear information to the reader and highlight separately the level of statistical significance relating to the comparison between liraglutide 1.2mg plus metformin/glimepiride plus metformin vs placebo plus metformin. In light of this and other rulings accepted, these leavepieces would be withdrawn.

However, Novo Nordisk appealed against the alleged breach of Clause 3.2 when the Panel decided that the presentation of the data was inconsistent with the SPC. The graph contained results from a subgroup of Nauck *et al* (LEAD 2) which was covered by the SPC. Although the HbA1c improvement in this subgroup could not be found specifically in the SPC, the observed results were consistent with the results revealed in the overall study population. The subgroup-specific HbA1c improvement was published in LEAD 2.

Novo Nordisk submitted that it was inappropriate and unjust for the Panel to rule a breach of Clause 3.2 of the Code when the same item was approved by the MHRA as being in compliance with Regulation 3A(1) of the Advertising Regulations and Paragraph 4.3 of the Blue Guide.

**COMMENTS FROM LILLY**

There were no comments from Lilly.

**APPEAL BOARD RULING**

The Appeal Board noted its comments and rulings in Point B1 above regarding the advertisement which it considered also applied here.

The Appeal Board noted that the chart had been ruled to be misleading. However, the Appeal Board considered that the patients in the study were treated in accordance with the licensed indication for Victoza. The Appeal Board did not consider that the presentation of the data was inconsistent with the Victoza SPC. The Appeal Board ruled no breach of Clause 3.2. The appeal on this point was successful.

**4 Leavepieces 'Get to the roots of the data on Victoza' (UK/LR/0409/0080 and UK/LR/0609/0201)**

The two leavepieces were similar to each other. Page 1, the front cover, of one of the leavepieces included the statement 'SMC Pending' (UK/LR/0609/0201) similar to the clinical folder in point B2 and one of the leavepieces in point B3. The other leavepiece (UK/LR/0409/0080) did not include this phrase.

The front cover of the leavepieces was headed 'Get to the roots of the data on Victoza' followed by the details of the indication.

Pages 2 and 3 formed a double page spread headed 'A strong spread of evidence supports Victoza' beneath which appeared detailed data Nauck *et al* (LEAD 2), Marre *et al* 2009 (LEAD 1) and Zinman *et al* (LEAD 4).

The data was divided into the following three sections: Victoza or glimepiride added on to metformin where data from Nauck *et al* (LEAD 2) and data on file were presented; Victoza or rosiglitazone added on to glimepiride where data from Marre *et al* (LEAD 1) and data on file were presented and Victoza or placebo added on to metformin + rosiglitazone where data from Zinman *et al* (LEAD 4) and data on file were presented. The leavepiece gave certain HbA1c data, weight change data, systolic blood pressure change data and hypoglycaemia data for each of the Victoza combinations.

Page 4, the back cover, of the leavepiece included the boxed text at issue in the advertisement at Point B1:

'Once-daily Victoza, in combination with metformin and/or a sulphonylurea, impacts on multiple factors associated with type 2 diabetes providing from baseline

- Reductions in HbA1c

And in addition

- Reductions in weight
- Reductions in systolic blood pressure
- Improvements in beta-cell function.'

**COMPLAINT**

Lilly referred to the comments made about the advertisement in Point B1 above which it alleged applied to the cover of the leavepiece.

Lilly further alleged that, with regard to pages 2 and 3 and as outlined previously, the discussion of weight and systolic blood pressure reduction misled the reader to consider liraglutide as an anti-obesity agent and an antihypertensive. Further, the reader could not assess the clinical significance of any reduction in body weight or systolic blood pressure in a meaningful manner without reference to baseline qualifications; this was misleading by omission and exaggerated the facts.

As outlined previously, the discussion of major and minor hypoglycaemic events, in the context of promotional materials, was misleading and potentially compromised patient safety as it understated the importance of any such event to the patient and their quality of life.

The table presented a 6.7mmHg reduction of systolic blood pressure associated with liraglutide 1.2mg and rosiglitazone plus metformin compared with placebo (rosiglitazone plus metformin) referenced to Zinman *et al* 2009 (LEAD 4). Lilly alleged that the figure of -6.7mmHg was incorrect

and therefore misleading. The results section of Zinman *et al* (LEAD 4) included confidence intervals which were omitted from the leavepiece. The inclusion of the confidence intervals would have provided the reader with important and clinically relevant qualification to the absolute numbers presented. Further, for the statistical comparison of the placebo and liraglutide groups, Zinman *et al* (LEAD 4) reported that the placebo-corrected difference in the blood pressure reduction in the 1.2mg liraglutide group was not 6.7mmHg, as stated in the leavepiece, but rather a reduction of 5.6mmHg.

Lilly referred to its comments about the advertisement in Point B1 above which it alleged applied to the similar claim on page 4 of the leavepiece.

Lilly alleged that all of the concerns outlined above also related to item number UK/LR/0609/0201. With respect to the latter, the concerns outlined in point B2 above were also relevant.

For the reasons outlined above Lilly alleged that this leavepiece was in breach of Clauses 2, 3.2, 7.2, 7.3, 7.4, 7.8, 7.10, 8.1 and 9.1 of the Code.

**RESPONSE**

Novo Nordisk referred to its comments with regard to the advertisement at Point B1 in relation to the page 1 of the leavepiece.

With regard to pages 2 and 3 Novo Nordisk submitted that the data about weight and/or blood pressure reductions did not imply that Victoza had an anti-obesity or antihypertensive indication. The indication for Victoza for the treatment of adult type 2 diabetics to achieve glycaemic control was quite clearly stated on the front of the leavepiece and in the prescribing information on page 4. Further, Novo Nordisk did not believe that the overall content emphasized weight reduction as an end point and as such did not allow Victoza's licensed indication to be misinterpreted.

Novo Nordisk referred to its previous comments regarding the discussion concerning major and minor hypoglycaemic events in the context of promotional materials.

Novo Nordisk disagreed that the reduction in blood pressure of 6.7mmHg with liraglutide 1.2mg and 5.6mmHg with liraglutide 1.8mg presented in the table was incorrect. These statements were neither incorrect nor misleading and, since there were no errors reported at all in the table, the inclusion of confidence intervals would be entirely inappropriate. Indeed all the data presented could have confidence intervals included but Novo Nordisk did not believe this was appropriate in this case. The systolic blood pressure values in the table were, as quite clearly stated in the column heading 'Mean SBP change from baseline (mmHg)' (emphasis added) and not differences vs placebo. The p-values clearly referred to the differences vs placebo (since it was only on these ANCOVA model values that the statistics were performed) and this was, again, clearly stated in the table. The placebo-corrected reduction in systolic blood pressure from Zinman *et al* was indeed 5.6mmHg but this was not referred to at all in the table (as the values in the table were mean changes from baseline) and so this was also not incorrect.

With regard to page 4 Novo Nordisk referred to its comments in Point B1 regarding the visual and the advertisement UK/LR/0609/0087.

Taking into account the above comments, Novo Nordisk disagreed that the leavepieces were in breach as alleged.

**PANEL RULING**

With regard to the front page the Panel did not consider that the allegations in Point B1 were entirely relevant given that the leavepiece now at issue had a different claim to that in the advertisement at issue in Point B1 above. The only relevant allegation related to the use of the lollipop tree. The Panel did not consider that the combination of the lollipop tree and the claim on the leavepiece 'Get to the roots of the data on Victoza' implied that Victoza could uproot type 2 diabetes and eliminate the illness. The Panel considered that its ruling of no breach of Clauses 3.2, 7.2, 7.4 and 7.8 at Point B1 also applied here.

The Panel noted that the indication for Victoza was given on the front cover of the leavepiece.

Pages 2 and 3 did not distinguish between the licensed indication and the benefits set out in Section 5.1 of the Victoza SPC. In this regard the Panel noted relevant comments in point A1 above. The data on pages 2 and 3 of the leavepiece appeared beneath the heading 'A strong spread of evidence supports Victoza'. In that regard the benefits of therapy had not been separated from or placed subsidiary to the main indication. A wider indication was implied. On balance the Panel considered that the data on pages 2 and 3 were presented in a misleading manner in that it appeared all the data was covered by the indication for Victoza and this was not so. A breach of Clauses 7.2 and 7.3 was ruled. The Panel did not consider that the data, in effect, promoted Victoza for unlicensed indications and thus no breach of Clause 3.2 was ruled.

With regard to the absence of information about baseline measurements the Panel considered that as all the data was presented and much of it was included in the SPC the absence of information about baseline values was not in itself misleading. P values were included or 'N/S'. No breach of Clauses 7.2 and 7.3 was ruled in this regard.

With regard to the hypoglycaemia data the Panel noted that in a column of data recording the events

per subject year, zero events were recorded for all doses of Victoza except Victoza 1.8mg combined with glimepiride (0.009 events/subject year). The Victoza SPC did not, in a table of adverse reactions, differentiate between episodes of major and minor hypoglycaemia. However the SPC stated that hypoglycaemia was common and very common when Victoza was used in combination with a sulphonylurea. Major hypoglycaemia had primarily been observed when combined with a sulphonylurea. The SPC further stated that most episodes of confirmed hypoglycaemia in clinical studies were minor. Major hypoglycaemia might occur uncommonly and had primarily been observed when Victoza was combined with a sulphonylurea (0.02 events/subject year). Very few episodes (0.001 events/subject year) were observed with administration of Victoza in combination with oral antidiabetics other than sulphonylureas. The Panel thus did not consider that the leavepiece accurately reflected the balance of evidence as stated in the SPC with regard to major hypoglycaemic events. A breach of Clauses 7.2 and 7.3 was ruled.

With regard to the presentation of the reduction of 6.7mmHg in systolic blood pressure for the combination of Victoza 1.2mg with metformin and rosiglitazone the Panel noted that no confidence intervals were included anywhere in the table. For each of the three combinations placebo data was given and in this instance there was a reduction of 1.1mmHg for placebo. Readers could thus easily calculate that the placebo corrected blood pressure reduction was 5.6mmHg. The Panel considered that although the table presented complex data which would need to be read carefully to be understood it was not misleading per se to omit the baseline data as alleged by Lilly. No breach of Clauses 7.2 and 7.3 was ruled. The data was not exaggerated in that regard. No breach of Clause 7.10 was ruled.

With regard to page 4 the Panel considered that this was different to the advertisement in Point B1 above. Although the wording of the claim:

'Once-daily Victoza, in combination with metformin and/or a sulphonylurea, impacts on multiple factors associated with type 2 diabetes providing from baseline

- Reductions in HbA1c

And in addition

- Reductions in weight
- Reductions in systolic blood pressure
- Improvements in beta-cell function.'

was the same unlike the advertisement at issue in Point B1 it did not appear beneath the claim 'Do more than lower blood glucose'. In the leavepiece now at issue the claim appeared on page 4 following pages detailing the indication and a presentation of detailed data. However the Panel still considered that the claim on Page 4 as a summary of the preceding data was not acceptable and its rulings in Point B1 regarding this claim also applied. These rulings were appealed.

The Panel considered its ruling regarding the use of the phrase 'SMC pending' in point B2 also applied here. The Panel did not consider that the leavepiece was disparaging and no breach of Clause 8.1 was ruled.

In relation to the leavepiece as a whole the Panel considered that high standards had not been maintained and a breach of Clause 9.1 was ruled. It did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use.

**APPEAL BY NOVO NORDISK**

Novo Nordisk submitted that since the Panel considered that its rulings at Point B1 applied here in relation to page 4 of the leavepiece, it repeated its position set out in B1. Novo Nordisk noted that as it had accepted other rulings, these leavepieces would be withdrawn.

**COMMENTS FROM LILLY**

There were no comments from Lilly.

**APPEAL BOARD RULING**

The Appeal Board noted its comments and rulings in Point B1 above regarding the advertisement which it considered also applied to page 4 of the leavepiece at issue.

**5 Leavepiece 'Dosing: use one device, once a day' (UK/LR/0409/0077)**

Page 1 of the leavepiece featured the picture of the lollipop tree and was headed 'Dosing: use one device, once a day' followed by 'Victoza allows convenient once-daily dosing at any time, independent of meals'.

Page 2 included a section headed 'Victoza can be used in combination with the following therapies'. This was followed by a chart which stated that 'no dose adjustments needed' for metformin or metformin plus thiazolidinedione.

**COMPLAINT**

Lilly alleged that the lollipop tree was misleading and inconsistent with the Victoza SPC and its licensed indication. Whilst the depiction of type 2 diabetes by analogy to a 'lollipop tree' was not unreasonable, the visual showed this tree being entirely uprooted. This implied that Victoza could uproot type 2 diabetes and eliminate it completely; Victoza would not cure diabetes as implied by the visual. Notwithstanding the latter, the visual also implied that Victoza delayed the progression of type 2 diabetes for which liraglutide was not licensed.

Lilly alleged that the heading 'Dosing: use one device, once a day' was ambiguous and misleading. Without reference to any other qualifying information on this page, the claim implied that Victoza could be used as monotherapy.

The claim that 'Victoza allows convenient once-daily dosing at any time, independent of meals' was ambiguous and inconsistent with Section 4.2 of the SPC which stated that '… it is preferable that Victoza is injected around the same time of day, when the most convenient time of day has been chosen'. This would suggest some regulatory and pharmacokinetic related restrictions and considerations around the need to establish and maintain the timing of injections; this was clearly at odds with the claim, which suggested that, day to day, patients could freely alter the time of their injection. The claim also appeared on page 3 of the leavepiece.

The statement on page 2 that 'No dose adjustments needed' with respect to metformin and metformin and thiazolidinedione when combined with Victoza was misleading and incorrect as it suggested that dose adjustments would never arise with respect to any component of these combinations; this was not consistent with the real-life clinical situation and the Victoza SPC.

For the reasons outlined above Lilly alleged that this leavepiece was in breach of Clauses 2, 3.2, 7.2, 7.3, 7.4, 7.8, 7.10, 8.1 and 9.1 of the Code.

**RESPONSE**

Novo Nordisk referred to its response in Point B1 regarding the visual. There was no intended suggestion of uprooting, eliminating or otherwise curing diabetes. The advertisement specifically summarised the impact of Victoza on physiological abnormalities seen in type 2 diabetes and called for physicians to consider more than blood glucose in their treatment.

Novo Nordisk did not agree that the headline 'Dosing: use one device, once a day' referred to anything other than the dosing and delivery of Victoza. Given that the claim did not refer to any concomitant treatment (all of which were oral treatments in any event), Novo Nordisk refuted that the claim implied that Victoza could be used as monotherapy.

The claim 'Victoza allows convenient once-daily dosing at any time, independent of meals' was not ambiguous and was consistent with the SPC which stated: 'Victoza is administered once daily at any time, independent of meals, and can be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site and timing can be changed without dose adjustment'. The comment in the SPC that 'However, it is preferable that Victoza is injected around the same time of the day, when the most convenient time of the day has been chosen' would refer to any medicine – no physician would recommend that a patient actively varied the time of administration of a medicine on a day-to-day basis since, at the very least, this could lead to missed doses and reduced adherence. However, there were no regulatory or pharmacokinetic related restrictions and considerations around the need to establish and maintain the timing of injections.

Novo Nordisk was confused by Lilly's allegation that the statement that 'No dose adjustments needed with respect to metformin and metformin + thiazolidinedione when combined with Victoza was inconsistent with the SPC. The SPC stated that 'Victoza can be added to existing metformin or to a combination of metformin and thiazolidinedione therapy. The current dose of metformin and thiazolidinedione can be continued unchanged'.

**PANEL RULING**

The Panel noted its rulings regarding the lollipop tree in Point B1 above which it considered applied here.

With regard to the claim 'Dosing: use one device, once a day' the Panel considered that the front page of the leavepiece was not sufficiently clear that Victoza was to be used in combination with oral antidiabetic agents rather than as monotherapy. The claim was misleading. A breach of Clause 7.2 was ruled. This ruling was appealed.

The Panel considered the claim 'Victoza allows convenient once-daily dosing at any time independent of meals' was ambiguous and misleading given the specific mention in the SPC that '… it is preferable that Victoza is injected around the same time of day, when the most convenient time of day has been chosen'. A breach of Clause 7.2 was ruled. This ruling was appealed.

With regard to page 2, the Panel noted that it was stated that when Victoza was administered with metformin or with metformin plus a thiazolidinedione, no dose adjustments were needed. The SPC stated that Victoza could be added to existing metformin or to a combination of metformin and thiazolidinedione therapy. The current dose of metformin and thiazolidinedione could be continued unchanged. The Panel thus did not consider that the statement in the leavepiece was misleading or incorrect as alleged. No breach of Clause 7.2 was ruled.

During its consideration of this matter the Panel was concerned that the statement 'Victoza can be used in combination with the following therapies' might be read as implying that combination therapy was optional and that Victoza could be used as monotherapy. The word 'can' implied a choice in that regard the Panel asked that Novo Nordisk be advised of its concerns.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. This ruling was appealed. The Panel was concerned that the leavepiece was not

clear about the indications for a new product and implied that it could be used as monotherapy. The Panel decided on balance that the leavepiece brought discredit upon the industry and a breach of Clause 2 was ruled. This ruling was appealed.

**APPEAL BY NOVO NORDISK**

Novo Nordisk submitted that whilst it might not have been instantly obvious from the front page, that Victoza was to be used in combination with oral antibiotic agents rather than as a monotherapy page 2 of the leavepiece focused on the licensed indication and the potential combinations in which Victoza could be used according to its licence. Novo Nordisk did not believe that health professionals would only read the front page of a leavepiece which contained information about dosing of a medicine, and thus the leavepiece should be considered as a whole. It was reasonable to expect that health professionals would read the information contained in the material before interpreting it and on that basis the leavepiece was not misleading.

Novo Nordisk noted that whilst it knew that Clauses 7.2 and 7.4 of the Code and Regulation 3A(2) and (3) of the Advertising Regulation and Paragraph 4.3 of the Blue Guide were not entirely equivalent, pre-vetting against such requirements took place. Novo Nordisk therefore did not agree with the Panel that the leavepiece was misleading and in breach of Clause 7.2.

Novo Nordisk disagreed with the Panel that 'Victoza allows convenient once-daily dosing at any time independent of meals' was ambiguous and misleading in light of the statement in the SPC that it was preferable for Victoza to be injected at the same time of day. The SPC stated that it was preferable to inject Victoza at the same time of the day, not that this was a requirement. The SPC required that Victoza was injected once a day. The SPC also indicated that it could be injected anytime of the day independent of meals. This requirement and the highlighted competitive advantage of Victoza vs exenatide (ie independent of meals) were reflected in the materials.

Novo Nordisk reiterated its comments above about pre-vetting and thus appealed the ruling of breach of Clause 7.2.

Novo Nordisk did not understand the rulings of a breach of Clause 9.1 and, particularly, the breach of Clause 2 in this case. Novo Nordisk submitted that even if it accepted the ruling relating to the front page, and leaving aside the fact that the MHRA had pre-vetted the materials, the item contained a clear indication how to use Victoza on page 2. Undoubtedly there was no intention to deliberately mislead the audience. Furthermore the lack of information about the preferred time of injection could not be considered as compromising patient safety. Using Victoza at the same time each day was a preference, not a necessity. Novo Nordisk noted that the US new drug application for Victoza did not require that the product carry this recommendation which might perhaps put it in some context.

On the basis of the above Novo Nordisk strongly disagreed with the Panel that this material was in breach of Clauses 9.1 and 2 of the Code.

**COMMENTS FROM LILLY**

Lilly alleged that Novo Nordisk's assertion that the claim 'Victoza allows convenient once-daily dosing at any time independent of meals' was inconsistent with the SPC and ambiguous. This unqualified claim was misleading and ignored the very specific instruction in the SPC regarding the need for patients to establish and adhere to the most convenient time of day for injecting liraglutide. Arguably, if this was not deemed to be an important aspect for safe use it was likely that its inclusion in the product label would not have been considered necessary by the licensing authorities.

**APPEAL BOARD RULING**

The Appeal Board considered that the claim 'Dosing: use one device, once a day', on the front page of the leavepiece, was not sufficiently clear that Victoza was to be used in combination with oral antidiabetic agents rather than as a monotherapy. In addition page 2 of the leavepiece stated that 'Victoza **can be** used in combination with the following therapies' (emphasis added) which implied an element of choice in the matter and reinforced the impression that Victoza could be used as a monotherapy. The Appeal Board considered that the claim at issue on the front page of the leavepiece was misleading and thus upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

The Appeal Board considered that despite the statement in the SPC that '…it is preferable that Victoza is injected around the same time of day when the most convenient time of day has been chosen' the claim 'Victoza allows once-daily dosing at any time independent of meals' was not ambiguous or misleading. Victoza was a once daily medicine and in that regard prescribers would expect there to be an approximate 24 hour gap between doses. The Appeal Board ruled no breach of Clause 7.2. The appeal on this point was successful.

The Appeal Board considered that although the leavepiece had been ruled in breach of Clause 7.2 it did not consider that there had been a failure to maintain high standards or that discredit had been brought upon the industry. The Appeal Board ruled no breach of Clauses 9.1 and 2. The appeal on these points was successful.

**C Patient Support Materials**

**1 Booklet 'Victoza Guide – Making a fresh start with Victoza' (UK/LIRA/0609/018)**

The front cover of the booklet included the

company name and logo as well as in the bottom right corner the claim 'New' followed by the product logo (brand name and generic name).

**COMPLAINT**

Lilly had a number of concerns regarding this booklet. The design, style and content was closely associated with that of the promotional materials discussed in point B above; this was therefore promotion of Victoza to patients. This was evidenced by the significant reliance on the liraglutide branding colours, inclusion of promotional messages and brand name throughout this booklet. For example, starting from the front cover, which referred to 'Victoza' three times, the booklet referred to the brand name no less than eighty-nine times! This went well beyond the legitimate purpose of product identification. To compound matters, injection needles manufactured by Novo Nordisk, NovoFine and NovoTwist, were also referred to by brand name.

The reference to new Victoza on the cover page was a promotional claim that was not relevant or appropriate for patients who had already been prescribed the medicine.

The last paragraph on page 5 informed patients that the risk of hypoglycaemia with Victoza was minimised due to its mode of action. This was not only inappropriate and irresponsible but clearly promoted Victoza to patients with regard to its safety. Lilly noted that having referred to hypoglycaemia, the booklet failed to inform or provide any guidance of how to manage the common occurrence of this important adverse event which might arise particularly when Victoza was combined with a sulphonylurea; this omission was clearly deliberate in order to minimise or understate the occurrence of hypoglycaemia with Victoza.

Page 8 of the booklet, informed about the posology and method of administration of Victoza and the timing requirements for the injection. The style and wording used was the same as that in the leavepiece UK/LR/0409/0077 (point B5 above); this showed that Novo Nordisk had employed this patient information booklet to promote Victoza.

Similarly, on page 18 of the booklet the promotional claim '… fit Victoza into your life better' was presented in an emboldened font. This showed that the Victoza patient support materials were being used as an advertising platform.

For the reasons outlined above Lilly alleged that the Victoza patient support materials were in breach of Clauses 2, 9.1, 12.1, 22.1, 22.2 and 22.5.

Lilly also believed that these patient support materials breached the MHRA Blue Guide on the Advertising and Promotion of Medicines in the UK, which prohibited the promotion of prescription only medicines to patients and the public.

**RESPONSE**

Novo Nordisk submitted that the booklet was designed and developed for patients who had been prescribed Victoza as support material to help with different aspects of their new treatment. As such, it could not be considered a promotional item.

Novo Nordisk disagreed that this material should have a detailed discussion on how to handle hypoglycaemic events. The booklet did not replace consultation with a health professional, thus the area of concern on how to deal with such an event should be covered in detail with the health professional. Furthermore the section about side effects clearly referred patients to the patient information leaflet which dealt with this issue.

**PANEL RULING**

The Panel did not consider that the fact that the design, style and content of material for patients was closely associated with the various promotional materials meant that the patient material was therefore unacceptable. What was important was whether such material met the requirements of Clause 22.

It was not unacceptable for patients prescribed a product to be given information about that product provided, as stated in the supplementary information to Clause 22.2, that such information was factual and non-promotional. The Panel was concerned that the front page of the patient booklet included the product logo plus the claim 'New'. This implied that the content was promotional. This impression was compounded by the positive statement 'Making a fresh start with Victoza'. Such promotional branding combined with a claim should not be used in patient materials. In the Panel's view the front page was, in effect, an advertisement for a prescription only medicine and a breach of Clause 22.1 of the Code was ruled. This ruling was appealed.

The Panel did not consider that it was unacceptable to refer to NovoFine and NovoTwist needles in relation to the section 'Prepare your pen'. Lilly had not given details as to where in the booklet references appeared. No breach of Clauses 22.1 and 22.2 was ruled.

Page 5 referred to 'The science bit' and stated that, because of the way Victoza worked, the risk of hypoglycaemia was minimised. Advice on how to cope with hypoglycaemia would have been helpful but as patients prescribed Victoza would have already been prescribed other medicines which could possibly cause hypoglycaemia, in that regard they should already know what to do. The Panel noted however that the Victoza SPC listed hypoglycaemia as a common event (in combination with both metformin and glimepiride) or a common event (in combination with either metformin and rosiglitazone or in combination with glimepiride alone). Clause 22.2 of the Code required that patient

material must not be misleading about the safety of a product. Given the statement in the Victoza SPC about hypoglycaemia, the Panel did not consider that to state that the risk of hypoglycaemia was minimised with Victoza was fair or balanced; it misled with regard to the safety of the product. A breach of Clause 22.2 was thus ruled.

Page 8 was headed 'Step-by-step injection guide' and stated 'You should inject Victoza only once a day, at any time of day, with or without eating food first. But it's best if you use Victoza at the same time every day – so pick a time you won't forget'. The Panel did not consider that this page of the booklet promoted Victoza to the public as alleged. That the style and wording bore similarities to the promotional item considered at point B5 above was not, in itself, unacceptable. The information was in line with the SPC unlike that in point B5 above. No breach of Clauses 22.1 and 22.2 were ruled.

The Panel did not consider that the statement on page 18 'Here are a few tips to help you fit Victoza into your life better' was a promotional claim. This section referred to the need to take medicine regularly in order to get the full benefits and referred readers to sources of help. The Panel did not consider that the page advertised Victoza to the public. Readers would have been prescribed the product. The information was not unreasonable. The Panel ruled no breach of Clauses 22.1 and 22.2.

The Panel noted its ruling of a breach of Clause 22.1 in relation to the front page. However, the Panel did not consider that overall the booklet was promotional material that had been disguised as information to patients. No breach of Clause 12.1 was ruled.

During its consideration of this point the Panel was concerned about the impression given by the front page about the origin of the material. 'freshstart Diabetes support from people like you' appeared prominently in the top left hand corner in the same font colour as the Victoza logo. In addition to the Victoza logo the brand name appeared twice below the freshstart logo. The only reference to Novo Nordisk was beneath the company logo which was blue and appeared in a very small font in the lower left hand corner. Patients might assume that the leaflet came from Freshstart which, from its description on the front page, appeared to be a patient organisation. The role of the company in producing the booklet or running the FreshStart Programme was not sufficiently clear. There was no allegation before the Panel on this point. The Panel requested that Novo Nordisk be advised of its concerns.

The Panel ruled no breach of Clause 22.5 which required that companies were responsible for information about products issued by their public relations agency. This was a statement of principle, it was not a requirement of the Code that could be breached.

With regard to Lilly's comments about the MHRA Blue Guide the Panel noted that it could only consider the allegations in relation to the Code and not the MHRA Blue Guide or UK law.

The Panel considered that the use of the Victoza logo and the claim 'new' meant that high standards had not been maintained and a breach of Clause 9.1 was ruled. The Panel did not consider that on balance the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use.

**APPEAL BY NOVO NORDISK**

Novo Nordisk noted that as it had accepted the ruling of the breach of Clause 22.2, it had withdrawn this booklet.

Novo Nordisk disagreed with the Panel that using a single product logo on material which was disseminated only to Victoza patients would make a 22 page booklet promotional. Novo Nordisk further noted that although the Panel noted its ruling of a breach of Clause 22.1 in relation to the front page, overall the Panel did not consider that the booklet was promotional material that had been disguised as information to patients.

Novo Nordisk submitted that as only existing users of Victoza would see the booklet and that the product packaging carried the Victoza logo, it did not understand how using the logo on the booklet made it promotional.

Novo Nordisk noted that the prohibition on use of the word 'new' in Clause 7.11 of the Code was limited to where a product had been generally promoted for more than 12 months in the UK. There did not seem to be any other relevant Code provision. Therefore it did not understand the Panel's objection to the use of the word, since Victoza had not been generally promoted for more than 12 months in the UK.

Novo Nordisk did not agree with the Panel that the patient booklet was in breach of Clause 22.1 of the Code.

**COMMENTS FROM LILLY**

There were no comments from Lilly.

**APPEAL BOARD RULING**

The Appeal Board considered that the use of the Victoza logo in combination with the claim 'New' promoted Victoza. This was compounded by the positive statement 'Making a fresh start with Victoza'. Such promotional branding combined with a claim should not be used in patient material. It was irrelevant that patients would know the brand name. In the Appeal Board's view the front page, was, in effect, an advertisement to the public for a prescription only medicine and it upheld the Panel's ruling of a breach of Clause 22.1 of the Code. The

appeal on this point was unsuccessful.

**2 Website 'www.MyDiabetesFreshStart.co.uk' (UK/LIRA/0509/001, 002, 003, 004, 005, 007)**

**COMPLAINT**

Lilly stated that it had a number of concerns regarding this website.

As discussed in point C1 above, the design, style and content of the website was such as to promote and advertise Victoza to patients. This was evidenced by the significant reliance on the product branding, promotional messages and numerous mentions of 'Victoza' throughout eg the webpage entitled 'Victoza FAQs' [frequently asked questions] referred to 'Victoza' twenty-three times; additionally 'Victoza' was used twenty-two times within the responses to the FAQs.

The points discussed above with regard to the booklet (point C1) were also pertinent to the webpage entitled 'About Victoza'.

For the reasons outlined above Lilly alleged that the website was in breach of Clauses 2, 9.1, 12.1 22.1, 22.2 and 22.5 of the Code.

Lilly also believed that the website breached the MHRA Blue Guide on the Advertising and Promotion of Medicines in the UK, which prohibited the promotion of prescription only medicines to patients and the public.

**RESPONSE**

Novo Nordisk stated that the website was developed as a post prescription site for patients already prescribed Victoza (access to the site was granted by using the barcode on the packaging), therefore the site was not promotional.

Novo Nordisk denied that the website was in breach of the clauses as alleged.

**PANEL RULING**

The Panel noted that its comments regarding the alleged breach of the MHRA Blue Guide in point C1 above also applied here.

The Panel did not accept Novo Nordisk's submission that as the site was developed for patients as a post prescription site it was not promotional. Whether the site was promotional depended, *inter alia*, on its content. Whilst patients for whom the prescribing decision had been made could be provided with information about their medicine, such information must not be promotional.

The Panel noted the comments it had made about the booklet at issue in point C1 above. The Panel noted that many of the webpages included the brand logo. The Panel considered that this was unacceptable and constituted the promotion of a prescription only medicine to the public. A breach of Clause 22.1 was ruled. This ruling was appealed. The Panel considered that in this regard high standards had not been maintained and a breach of Clause 9.1 was ruled. This ruling was appealed. However, the Panel did not consider that overall the booklet was promotional material that had been disguised as information to patients. No breach of Clause 12.1 was ruled. On balance the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use.

The Panel noted that Lilly had not provided detailed allegations about the webpage entitled 'About Victoza' it had relied on its allegations in point C1 above. It was not for the Panel to identify Lilly's allegations based on this cross reference approach. Insufficient detail had been provided thus the Panel decided not to rule on this general allegation. If Novo Nordisk accepted the Panel's rulings regarding point C1 it would have to check the website to ensure that any similar material was withdrawn as would be required by signing the requisite form of undertaking.

The Panel ruled no breach of Clause 22.5 which required that companies were responsible for information about products issued by their public relations agency. This was a statement of principle, it was not a requirement of the Code that could be breached.

**APPEAL BY NOVO NORDISK**

Novo Nordisk disagreed with the Panel's rulings and noted that the Panel stated that whether a website was promotional depended, *inter alia*, on its content and did not consider the overall material was promotional. Where the overall material was not promotional, it was hard to see how using the product logo on a webpage which was dedicated to Victoza-users made the webpage promotional. Furthermore, as mentioned in C1 above, the Victoza logo was on the product packaging. This could only be accessed by patients already using the product and Novo Nordisk reiterated the point made in C1 in this regard.

Novo Nordisk further submitted that it was inappropriate and unjust for the Panel to rule a breach of Clause 22.1 of the Code when the same item was approved by the MHRA as being in compliance with paragraph 5.2 of the Blue Guide.

Novo Nordisk therefore did not agree with the Panel that the website was in breach of either of Clauses 22.1 or 9.1 of the Code.

**COMMENTS FROM LILLY**

There were no comments from Lilly.

**APPEAL BOARD RULING**

The Appeal Board noted the comments it had made

about the booklet at issue at Point C1 above. Unlike the booklet the web pages now at issue did not include the claim 'New'. 'Fresh start' appeared as the name of the patient programme, which in the Appeal Board's view did not have the same effect as a claim 'Making a fresh start with Victoza' which was used in the booklet at issue in Point C1. The Appeal Board was concerned that the brand name was used frequently. However it did not consider that the web pages constituted the promotion of a prescription only medicine to the general public. The Appeal Board ruled no breach of Clause 22.1 and in that regard considered that Novo Nordisk had not failed to maintain high standards. The Appeal Board ruled no breach of Clause 9.1. The appeal on both points was successful.

**D Liraglutide Formulary Pack**

In response to these allegations Novo Nordisk had provided the Liraglutide Formulary Pack (UK/LR/0609/0218) dated July 2009. This consisted of four sections and appeared to include a set of slides and was considered by the Panel as follows.

**1 Section 1 - 'The burden of type 2 diabetes'**

**COMPLAINT**

Section 1.1, 'Executive summary', consisted of a number of bullet points which included the following:

> 'There are a number of unmet challenges in the management of T2D [type 2 diabetes], including inadequate glycaemic control, blood pressure control and treatment adherence.
>
> In addition, many currently available therapies are associated with significant limitations, such as hypoglycaemia and weight gain.
>
> There is therefore a need for novel treatments that address current unmet needs.
>
> Novo Nordisk is a world leader in the development of treatments for diabetes ....'.

Lilly alleged that these statements, in support of the promotion of Victoza, were misleading, could not be substantiated, exaggerated the facts and invited a comparison of Victoza with other antidiabetic agents with respect to efficacy and safety. Novo Nordisk asserted that compared with other, undefined, antidiabetic agents its novel treatment Victoza addressed an unmet need with respect to achieving adequate glycaemic control, no weight gain, improved treatment adherence and an improved side-effect profile with particular regard to the incidence of hypoglycaemia; this claim was disparaging, could not be substantiated and exaggerated the facts with respect to treatments such as Byetta. Further, the claims implied that Victoza also fulfilled an unmet need with respect to reductions in blood pressure and weight, for which it was not licensed.

The above assertions were also evidenced by the content of Section 1.6, 'Unmet challenges in T2D treatment', which included statements such as 'Despite advances in the management of T2D, current treatment options have important deficiencies. These include hypoglycaemia as a potential adverse event, and a high risk of weight gain'. This sweeping generalisation invited a misleading comparison of Victoza with different classes of antidiabetic agents some of which might be the only option for individual patients eg those who required insulin due to beta-cell failure. The section then went on to discuss various 'unmet challenges' with particular reference to 'Beta-cell decline and glucose control', 'BMI and weight', 'Hypoglycaemia', 'Blood pressure' and 'Treatment adherence'. Given the context of the discussion regarding unmet needs, Lilly was surprised that the reader was not also informed about the availability of Byetta which was the first-in-class GLP-1 receptor agonist and which addressed all of the unmet challenges referred to in this section; this misled the reader by omission. The statement in Section 1.6.4, 'Blood pressure', that 'Most treatments for T2D do not affect systolic blood pressure' further demonstrated Novo Nordisk's intention to discuss Victoza as an anti-hypertensive treatment; an unlicensed indication.

In Section 1.7, 'Novo Nordisk: A world leader in diabetes care', the statement that Victoza was '... the first once-daily human glucagon-like peptide-1 (GLP-1) analogue developed for the treatment of T2D' misled the reader by omission. In the absence any mention of Byetta the impression created was that liraglutide was the first licensed product in this particular class.

Section 1.8, 'Conclusion', reinforced the statements, discussed above which were misleading, not capable of substantiation, exaggerated the facts and disparaged other antidiabetic agents, and in particular Byetta, with respect to their efficacy and safety as compared to liraglutide.

For the reasons outlined above Lilly alleged that sections were in breach of Clauses 2, 3.2, 7.2, 7.3, 7.4, 7.8, 7.9, 7.10, 8.1, 9.1 and 10.2 of the Code.

**RESPONSE**

Novo Nordisk stated that the statements at issue were general statements in the introduction to the pack which set the scene regarding the unmet challenges with regard to the treatment of type 2 diabetes and had been taken out of context. There were no claims in this section that Victoza, or any other treatment could eliminate these challenges. There were no comparisons direct or indirect between Victoza and other antihyperglycaemic agents in this section. Thus Novo Nordisk did not agree with Lilly's allegation that the statements in context with Victoza were misleading and not capable of substantiation.

Section 1.6: Novo Nordisk noted Lilly's statement that Byetta addressed all of the unmet challenges described in the section. Novo Nordisk believed that GLP-1 analogues as a class might address the unmet challenges although to different extents. The intended context of this introductory section was to set the scene as to the challenges with regard to the treatment of type 2 diabetes, rather than to detail the extent to which each GLP-1 analogue could address these challenges. As such, it was intentional that no particular products were mentioned in this general introductory section.

Liraglutide was only mentioned in the last paragraph of Section 1.7, 'Novo Nordisk: A world leader in diabetes care', and not in relation to any promotional or therapeutic claim. Section 2.5 'The Lead Programme', was dedicated to the randomized clinical trials with liraglutide and provided details about the randomised controlled trial comparison of Victoza and Byetta (Buse *et al* 2009 (LEAD 6)). Therefore providing a balanced view within the pack. Novo Nordisk believed it was reasonable to suppose that the target audience (budget holders) read the whole document and received the relevant information about both products and their comparison and not just Section 1 in order to obtain information regarding type 2 diabetes.

Section 1.7: Novo Nordisk disagreed with Lilly that the statement 'liraglutide, the first once-daily human glucagon-like peptide-1 (GLP-1) analogue developed for the treatment of T2D' was misleading. Liraglutide was the first once-daily human glucagon-like peptide analogue developed for the treatment of type 2 diabetes.

Section 1.8: This section provided a short conclusion and provided a general summary of the challenges with the treatment of type 2 diabetes; as such Novo Nordisk referred to its comments with regard to Sections 1.1, and 1.6 above.

**PANEL RULING**

The Panel considered that Sections 1.1 to 1.6 constituted a general discussion on the burden of type 2 diabetes. General comments were made about what was described as 'important deficiencies' of currently available therapies. Nonetheless, these sections were an integral part of the formulary pack; the Victoza logo with the word 'new' appeared on the front cover of the section. There was thus, at the very least, an expectation in the mind of the reader that Victoza as a 'new' medicine would not have the deficiencies associated with current therapy. Such an expectation was compounded by statements such as 'prevention of weight gain **must** be a target for treatment alongside glycaemic control.' (emphasis added), (Section 1.6.2). The Panel considered that the purpose of Section 1 overall was, *inter alia*, to establish a need for those additional benefits which might be provided by Victoza and to state where current therapies failed. The challenge of BMI and weight was given equal emphasis to glycaemic control. The Panel considered that the section implied that Victoza would positively address all of the unmet challenges. The Panel noted its comments and rulings above on Victoza's effect on secondary benefits. Breaches of Clauses 3.2, 7.2, 7.3, 7.4 and 7.10 were ruled.

The Panel considered that the description of the unmet challenges in type 2 diabetes treatment in Section 1.6 'Unmet challenges' and Section 1.8 'Conclusion' could also be interpreted as implying that no product currently available met any one of these challenges. The Panel considered that this was misleading as the challenges and the differences between current treatments were not defined in detail. The Panel considered that this section was too general and thus misleading, it disparaged current treatments and the impression given was not capable of substantiation. A breach of Clauses 7.2, 7.3, 7.9, 7.10 and 8.1 was ruled in relation to Section 1.6 and Section 1.8.

The Panel noted that Victoza was described as 'the first once-daily human glucagon-like peptide-1 (GLP-1) analogue developed for the treatment of T2D' in Section 1.7. The Panel noted, however, that although Victoza was the first **once daily** human GLP-1 analogue it was in fact the second GLP-1 analogue to be marketed. In that regard the Panel considered that the statement was ambiguous and thus misleading. It was unclear as to which part of the statement 'first' applied to. A breach of Clause 7.2 was ruled. This ruling was appealed.

The Panel noted that Lilly had alleged a breach of Clauses 7.8 and 10.2 of the Code without giving any details of what was the subject of the allegations. In the circumstances the Panel considered that insufficient detail had been provided by Lilly and thus no breach of Clauses 7.8 and 10.2 were ruled.

The Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use.

**APPEAL BY NOVO NORDISK**

Novo Nordisk accepted the ruling of a breach of Clause 3.2, but on the basis that there was no objection in principle to the provision of background information about the company in promotional material. The formulary pack had been withdrawn.

Novo Nordisk submitted that the proximity of the adjective 'first' to the wording of 'once-daily' in the claim that Victoza was 'the first once-daily human glucagon-like peptide-1 (GLP-1) analogue' inevitably led to the interpretation that this was what the adjective related to. Liraglutide was the first GLP-1 analogue which could be injected once-daily, since exenatide should be injected twice, and the

statement was not misleading.

It was inappropriate and unjust that the Panel ruled a breach of Clause 7.2 of the Code as the item was approved by the MHRA as being in compliance with Regulation 3A(2) and (3) of the Advertising Regulation and Paragraph 4.3 of the Blue Guide.

Therefore Novo Nordisk did not agree with the ruling by the Panel that the claim was in breach of Clause 7.2 of the Code.

**APPEAL BOARD RULING**

The Appeal Board noted that Victoza was described as 'the first once-daily human glucagon-like peptide-1 (GLP-1) analogue developed for the treatment of T2D' in Section 1.7 of the formulary pack. The Appeal Board considered that Victoza was the first **once daily** human GLP-1 analogue. The statement was not ambiguous or misleading, as 'first' immediately preceded 'once daily' it clearly referred to that. The Appeal Board ruled no breach of Clause 7.2. The appeal on this point was successful.

**2 Section 2 - 'Clinical overview of liraglutide'**

**COMPLAINT**

Section 2.1, 'Executive Summary' included the statement that liraglutide was '… the first once-daily human glucagon-like peptide (GLP)-1 analogue …' and Lilly alleged that this misled the reader by omission. In the absence of any mention of Byetta the impression created was that liraglutide was the first licensed product in this particular class.

The claim that 'Liraglutide is administered once daily and can be given at any time of day, independently of meals …' was alleged to be ambiguous and inconsistent with Section 4.2 of the Victoza SPC as outlined above in point B5.

Again, the weight reduction and blood pressure reduction benefit associated with Victoza were discussed as though this were a licensed indication and not a secondary/additional benefit of the treatment after achieving glycaemic control. The misleading aspect of the latter was as discussed above in points B3 and B4. Lilly referred to Section 2.1 and Sections 2.5.2, 'Liraglutide and body weight', and 2.5.3, 'Liraglutide and SBP', stating that the latter was one of the boldest examples of inviting consideration of Victoza as a licensed treatment for systolic hypertension.

Section 2.3, 'Pharmacology and pharmacokinetics', discussed the importance of Victoza and beta-cell function and stated that 'Beta-cell function is important in the progression of T2D; many current therapies do not address this issue'. This unqualified statement invited a comparison with all antidiabetic agents and asserted that only Victoza improved beta-cell function, unlike agents such as Byetta, and positively impacted the progression of type 2 diabetes. There was no clinical evidence that Victoza delayed or halted the progression of type 2 diabetes. This disparaging claim could not be substantiated, and exaggerated the facts. In this particular regard, the statement that 'Data from animal studies demonstrated a significant increase in beta-cell mass after 6 weeks of liraglutide compared with controls' proposed a putative mechanism by which Victoza effected the implied delay or halt in disease progression in patients with type 2 diabetes. This assertion was misleading and could not be substantiated and implied that Victoza changed non-functional beta-cells into cells which could produce insulin. This claim also relied on extrapolating and exaggerating the clinical significance and relevance of data derived from animal studies to patients.

Section 2.4.4, 'Method of administration' invited a comparison with Byetta with respect to posology and method of administration. Lilly stated that as per its comments above about Section 2.1, the statement 'In contrast to twice-daily exenatide, liraglutide can be administered once daily, independent of mealtimes and can be taken at any time of the day' was misleading and inconsistent with the Victoza SPC.

Sections 2.5.5, 'Safety and tolerability', 2.5.5.1 'Hypoglycaemia', and 2.5.5.2 'Adverse events', discussed the incidence and severity of hypoglycaemia with reference to results from Buse *et al* (LEAD 6). Lilly's concerns outlined with regard to Section 2.5 were applicable here. Lilly noted that the discussion of the comparative incidence of nausea in Buse *et al* (LEAD 6) was reported as being similar for Victoza and Byetta but the reader was additionally told that the '… nausea persisted longer with exenatide than with liraglutide' which was unbalanced and misleadingly implied that no liraglutide subjects experienced nausea at the 26 week study end time-point.

In Section 2.6, 'Conclusion', the statements that '… liraglutide could be particularly useful if weight gain is a concern' and 'As majority of patients with T2D have hypertension, the reduction of SBP with liraglutide should be beneficial to most patients' clearly misled readers to consider Victoza as a licensed treatment for systolic hypertension and obesity. Indeed, to compound matters, Section 2.7, 'Frequently asked questions', offered a putative mechanism by which Victoza might reduce blood pressure.

For the reasons outlined above Lilly alleged that these sections were in breach of Clauses 2, 3.2, 7.2, 7.3, 7.4, 7.8, 7.9, 7.10, 8.1, 9.1 and 10.2.

**RESPONSE**

Novo Nordisk submitted that the statement 'the first once-daily human glucagon-like peptide (GLP) - analogue' in Section 2.1 was not misleading and was capable of substantiation as evidenced by the

difference between the Victoza and Byetta SPCs. Novo Nordisk also believed the claim regarding the administration of Victoza reflected the SPC, which stated at Section 4.2 that it could be administered 'at any time'. Novo Nordisk referred to its comments in point B5 above.

With regard to the allegation about information on weight reduction, Novo Nordisk referred to its response in relation to points B3 and B4 above.

In addition Novo Nordisk stated that the discussion of the effect of liraglutide on weight and systolic blood pressure in Section 2.3 was derived from pre-specified endpoints of six large, randomised, controlled clinical trials (Marre *et al* 2009 (LEAD 1), Nauck *et al* 2009 (LEAD 2), Garber *et al* 2008 (LEAD 3), Zinman *et al* 2009 (LEAD 4), Russell-Jones *et al* 2009 (LEAD 5) and Buse *et al* 2009 (LEAD 6)), all of which had been published in peer reviewed journals. Using this data as evidence of liraglutide's full therapeutic effect was entirely appropriate and provided clinicians and budget holders with relevant information to help them make a rational assessment of Victoza's characteristics. There was no claim or inference that weight management or blood pressure control were licensed indications.

The statement 'Beta-cell function is important in the progression of T2D; many current therapies do not address this issue' was sufficiently qualified with regard to the nature of the findings, in terms of beta-cell mass (animal data, in vitro data, Sturis *et al* 2003). It was reasonable to point out that such findings might have clinical implications (delay/halt disease progression) as highlighted in the document. Further, it was true that other therapies did not address this issue.

Section 2.4.4: Novo Nordisk did not agree with Lilly that the statement 'In contrast to twice-daily exenatide, liraglutide can be administered once daily, independent of mealtimes and can be taken at any time of the day' was misleading and inconsistent with the liraglutide SPC. This statement simply reflected the differences between the Byetta and Victoza SPCs. Novo Nordisk also referred to its response in relation to Section 2.1 above.

Sections 2.5.5, 2.5.5.1, 2.5.5.2: With regard to Lilly's concern the fact that nausea in Buse *et al* (LEAD 6) persisted longer with Byetta than with Victoza, Novo Nordisk referred to Buse *et al* (LEAD 6) that 'although the incidence of nausea was similar initially, it was less persistent with liraglutide'. Therefore Novo Nordisk disagreed with the allegation regarding these sections and referred to its response in relation to Section 2.5 above.

Section 2.6: With regard to Lilly's concerns that the statements 'liraglutide could be particularly useful if weight gain is a concern' and 'As majority of patients with T2D have hypertension, the reduction of systolic blood pressure with liraglutide should be beneficial to most patients' were misleading and led readers to believe liraglutide was a licensed treatment for systolic hypertension and obesity, Novo Nordisk submitted that the statements had been taken out of context. Section 2.6 was a conclusion section, which started by noting the glycaemic efficacy and only mentioned potential weight loss and a drop of systolic blood pressure as added benefits of Victoza, which 'could' and 'should', not 'will' benefit patients. It was also clear when Section 3 was read as a whole that these conclusions were in relation to the findings of the study rather than the licensed indication of Victoza.

**PANEL RULING**

The Panel considered that its ruling of a breach of Clause 7.2 in point D1 above regarding the claim 'first once-daily human glucagon-like peptide (GLP)-1 analogue' also applied here.

The Panel considered that in Section 2.1 the bullet point 'Liraglutide is administered once daily, and can be given at any time of day, independently of meals …' was similar to a claim at issue point B5 above in that the detailed advice in the SPC that '… it is preferable that Victoza is injected around the same time of day, when the most convenient time of day has been chosen' was not included. The Panel therefore ruled a breach of Clause 7.2 of the Code. This ruling was appealed.

The Panel noted that in Section 2.1 the second bullet point referred to Victoza's indication and the sixth bullet point referred to improvements in glycaemic control; this was immediately followed by another bullet point 'Significant weight loss in comparison with comparator drugs when liraglutide was used in combination treatment'. Section 2.4 'Indication and dosing' clearly set out the approved indication. The Panel noted that Section 2.5 'The LEAD Programme' ended with the sentence 'The clinical benefits of treatment with liraglutide observed with LEAD trials are reported here'. Sub-section 2.5.1 'Liraglutide and glycaemic control' was immediately followed by Section 2.5.2 'Liraglutide and body weight'. Sub-section 2.5.3 'Liraglutide and SBP' referred to reductions in blood pressure. The Panel considered that although the approved indication was given almost at the outset of Section 2 ie glycaemic control, additional benefits of therapy (effect on body weight and blood pressure) were given equal emphasis. They were not unequivocally distinguished from the main goal of therapy. In that regard the Panel did not consider that the secondary benefits were adequately placed within the context of Victoza licensed indication. A breach of Clause 3.2 was ruled. This ruling was appealed.

The Panel noted that the final paragraph of Section 2.3, 'Pharmacology and pharmacokinetics', discussed the data regarding the effect of Victoza on beta-cell function. It was stated that there was evidence to suggest that liraglutide improved and protected beta-cell function. It was further stated that beta-cell function was important in the progression of type 2 diabetes and that many

current therapies did not address this issue. In that regard the Panel did not consider that Section 2.3 implied that only Victoza improved beta-cell function as alleged. The fact that many current therapies did not address the issue implied that some did. In that regard the Panel did not consider that the statement was misleading or exaggerated; nor did it disparage other therapies. No breach of Clauses 7.2, 7.4, 7.10 and 8.1 were ruled.

The Panel was concerned, however, that the discussion about beta-cell function did not explain the clinical significance of the findings. Although Victoza had been shown to improve beta-cell function there was no data to show that this altered the clinical course of type 2 diabetes. Some readers might assume that the data meant that Victoza delayed or halted the progression of the disease. In this regard the Panel considered that the information given was misleading and that its clinical importance had been exaggerated. A breach of Clause 7.2 and 7.10 was ruled.

The Panel noted that Section 5.1 of the Byetta SPC stated that clinical studies with Byetta had indicated improved beta-cell function based on measures such as the homeostasis model assessment and the proinsulin to insulin ratio and that improved first and second phase insulin secretion after 52 weeks of Victoza was demonstrated in a subset of type 2 diabetics. The Panel did not consider that failure to specifically mention Byetta's effect on beta-cell function in Section 2.3 of the formulary pack was in itself misleading and no breach of Clause 7.2 was ruled.

With regard to Section 2.4.4 'Method of administration' the Panel considered that the comparison that 'In contrast to twice-daily exenatide, liraglutide can be administered once daily, independent of mealtimes and can be taken at any time of the day' was misleading. Although the information from the SPC that it was preferable that Victoza was injected around the same time of day when the most convenient time of day was chosen appeared later in the paragraph the Panel considered that it was misleading and inconsistent with the SPC to not state this immediately following the comparison with exenatide. A breach of Clauses 3.2, 7.2 and 7.3 was ruled. These rulings were appealed.

Section 2.5, 'The LEAD Programme', stated that Buse *et al* (LEAD 6) was the first study to provide a direct comparison between the two GLP-1 receptor agonists and that the study compared 1.8mg liraglutide added to metformin and/or glimepiride versus 10mcg exenatide. The Panel did not consider that Section 2.5 was misleading as alleged. The limited information about Buse *et al* (LEAD 6) did not claim differences between the products it merely listed this study as contributing to the clinical data. No breach of Clauses 7.2 and 7.3 was ruled.

The Panel noted that Section 2.5.5.1' 'Hypoglycaemia', went into more detail than Section 2.5 in relation to outcomes from Buse *et al* (LEAD 6). There was insufficient detail about the nature of Buse *et al* (LEAD 6) which the Panel considered should have been included – particularly with regard to the doses of Victoza and Byetta used and the fact that the study was open label. Insufficient detail had been provided and thus the claim regarding differences in hypoglycaemia was misleading. A breach of Clauses 7.2 and 7.3 was ruled. These rulings were appealed.

Section 2.5.5.2 'Adverse events' included details of the data for nausea from the LEAD studies. In Buse *et al* (LEAD 6) the difference in the proportion of patients with nausea at 26 weeks on liraglutide 1.8mg (3%) and exenatide (9%) was statistically significant $p<0.0001$. The Panel did not consider the claim that nausea persisted longer with exenatide than liraglutide implied that no patient experienced nausea at 26 weeks. A preceding sentence described it as one of the most frequently reported adverse events. No breach of Clauses 7.2 and 7.3 was ruled.

Section 2.6 'Conclusion' referred to reductions in HbA1c and the second paragraph commenced:

> 'The effective management of patients with T2D requires achievement of glycaemic control as well as reductions in cardiovascular risk factors. Treatment with liraglutide led to weight loss that was greatest in patients with a higher baseline BMI and occurred irrespective of nausea, suggesting that liraglutide could be particularly useful if weight gain is a concern. As the majority of patients with T2D have hypertension, the reduction of SBP with liraglutide should also be beneficial to most patients'.

The Panel noted the comments made previously about changes in weight. Section 2.6 implied that all patients would lose weight and this was not so. However the Panel did not consider that this section would mislead readers to consider liraglutide as a licensed treatment for hypertension and obesity as alleged. No breach of Clause 7.2 was ruled.

The Panel noted that Lilly had alleged a breach of Clauses 7.8 and 10.2 of the Code without giving any details of what was the subject of the allegations. In the circumstances the Panel considered that insufficient detail had been provided by Lilly and thus no breach of Clauses 7.8 and 10.2 was ruled.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. This ruling was appealed. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use.

**APPEAL BY NOVO NORDISK**

Novo Nordisk submitted that its appeal relating to

the ruling in D1 regarding the claim 'first once-daily human glucagon-like peptide (GLP)-1 analogue' also applied here. Novo Nordisk submitted that its appeal in Point B5 was relevant to its appeal of the breach of Clause 7.2 in relation to Section 2.1 and the time of injection of Victoza.

Novo Nordisk disagreed with the Panel that Section 2 was in breach of Clause 3.2 of the Code. This ruling had been made on the basis that, despite the approved indication being given almost at the outset of Section 2, the additional benefits were given equal emphasis. Novo Nordisk submitted that this was not so. As noted by the Panel, Section 2 started with the licensed indication of Victoza and two of the early subsections (2.1 and 2.4) clearly indicated the licensed indication; it was only later in Section 2 that the additional benefits were described.

Novo Nordisk noted that the Panel considered Section 2.4.4 was misleading and inconsistent with the SPC as it did not state the information from the SPC that it was preferable that Victoza was injected around the same time of the day immediately following the comparison with exenatide that, in contrast to exenatide, liraglitude could be administered once daily, independent of mealtimes and at any time of day. Novo Nordisk referred to its appeal in Point B5 which was relevant here to explain why it did not agree that the statement in the formulary pack was inconsistent with the SPC. Additionally, the information that it was preferable to inject Victoza at the same time each day was, in any event, provided later on in the same paragraph. Novo Nordisk submitted that the Panel's view that there was a breach simply because the information was later in the same paragraph, but not immediately after the statement, suggested that someone would ready only part of the paragraph; this seemed irrational. Novo Nordisk therefore disagreed with the Panel that Section 2.4.4 was in breach of Clauses 3.2, 7.2 and 7.3.

Novo Nordisk noted that the Panel considered that reporting of the hypoglycaemia results from LEAD 6 (Base *et al*) Section 2.5.5.1 was misleading due to the lack of information about the open-label nature of the trial, and the lack of clarification of the investigated Victoza and exenatide doses. Novo Nordisk noted that both compounds were used at their maximum recommended doses. The detection of the hypoglycaemic risk difference, was thus conducted using a fair, scientifically valid comparison. If the applied doses had not been comparable, the Panel's view would have been more relevant. Furthermore, Novo Nordisk failed to understand what impact the clarification of the open-label nature of the trial would have on the interpretation of the hypoglycaemic risk difference. More importantly Section 2.5 stated that a detailed description of the LEAD trials was provided at the end of Section 2, in the Appendix. For each LEAD programme, the main results were reported in Section 2.5 and detailed information about the design of each was provided in the Appendix.

Novo Nordisk did not agree with the Panel that Section 2.5.5.1 was misleading in breach of Clauses 7.2 and 7.3.

Novo Nordisk submitted that Section 2 complied with the spirit of the Code and did not breach any of the clauses ruled by the Panel. High standards had been maintained and Novo Nordisk therefore also disagreed with the Panel's ruling of a breach of Clause 9.1.

**COMMENTS FROM LILLY**

Lilly alleged that the claim that 'Victoza is the first once-daily human glucagon-like peptide (GLP)-1 analogue' was unclear and, intended to mislead the reader. The wording did not leave any opportunity for the reader, uninformed about Byetta, to consider anything but the assertion that Victoza was the first (GLP)-1 analogue to be licensed.

Whilst not materially relevant to this particular case, Lilly noted the serious breaches of Code in respect of Case AUTH/2234/5/09 and Case AUTH/2269/9/09 involving the promotion of liraglutide by Novo Nordisk. Lilly alleged this evidenced the continued and flagrant disregard by Novo Nordisk of both the spirit and tenet of the Code.

**APPEAL BOARD RULING**

The Appeal Board noted its comments and ruling of no breach of Clause 7.2 in Point D1 above regarding the claim 'first once-daily human glucagon-like peptide (GLP)-1 analogue' also applied here.

The Appeal Board considered that in Section 2.1 the bullet point 'Liraglutide is administered once daily, and can be given at any time of day, independently of meals …' was similar to the claim at issue Point B5 above. The Appeal Board considered that its comments and ruling of no breach of Clause 7.2 of the Code in Point B5 also applied here.

The Appeal Board noted that in Section 2.1 the second bullet point referred to Victoza's indication and the sixth bullet point referred to improvements in glycaemic control; this was immediately followed by the seventh bullet point 'Significant weight loss in comparison with comparator drugs when liraglutide was used in combination treatment'. Section 2.4 'Indication and dosing' repeated the indication. The Appeal Board noted that Sections 2.5.1 'Liraglutide and glycaemic control' was immediately followed by Section 2.5.2 'Liraglutide and body weight' and Section 2.5.3 'Liraglutide and SBP'. The Appeal Board considered that although the approved indication was given almost at the outset of Section 2 ie glycaemic control, additional benefits of therapy (effect on body weight and blood pressure) were given equal emphasis. They were not unequivocally distinguished from the main goal of therapy. In that regard the Appeal Board did not consider that the secondary benefits were adequately placed within the context of Victoza's licensed indication. The Appeal Board upheld the

Panel's ruling of a breach of Clause 3.2. The appeal on this point was unsuccessful.

With regard to Section 2.4.4 'Method of administration' the Appeal Board considered that the comparison 'In contrast to twice-daily exenatide, liraglutide can be administered once daily, independent of mealtimes and can be taken at any time of the day' was not misleading. The information from the SPC that it was preferable that Victoza was injected around the same time of day when the most convenient time of day was chosen appeared later in the same paragraph. The Appeal Board ruled no breach of Clauses 3.2, 7.2 and 7.3. The appeal on this point was successful.

The Appeal Board noted that Section 2.5.5.1 'Hypoglycaemia', went into more detail than Section 2.5 in relation to outcomes from Buse *et al* (LEAD 6). The Appeal Board considered that it was not necessary to provide greater detail about Buse *et al* (LEAD 6). Both Victoza and Byetta were used at maximum dosage. In the context of the data the Appeal Board considered that the comparison regarding differences in hypoglycaemia was not misleading. The Appeal Board ruled no breaches of Clauses 7.2 and 7.3. The appeal on this point was successful.

The Appeal Board noted all the rulings regarding Section 2 of the formulary pack and did not consider that Novo Nordisk had failed to maintain high standards. The Appeal Board ruled no breach of Clause 9.1. The appeal on this point was successful.

**Section 3 - 'Health economic evaluation'**

**COMPLAINT**

Section 3.1 introduced cost-efficacy claims in support of Victoza with respect to weight reduction and reduction in blood pressure. This invited the reader to consider the cost-benefit of liraglutide in the context of a licensed treatment for obesity and systolic hypertension; this was misleading and inconsistent with the SPC. Indeed, the fact that changes in systolic blood pressure and body mass index had been included as 'Clinical inputs' in the economic modelling to support the cost-effectiveness of Victoza was evidenced in Tables 3.2 and 3.3. This indicated that other payor materials using this flawed economic modelling were also in breach of the Code. The rationale supporting the claim of a favourable cost implication of initiating Victoza and the need for self-monitoring of blood glucose (SMBG) was flawed, misleading and inconsistent with the Victoza SPC and real-life clinical practice.

Section 3.6 again misled by using the wording '… any time of day ...' with regard to the precise posology and method of administration as defined in the Victoza SPC. The reader was also invited to consider the cost advantage conferred by Victoza in that, when it was combined with oral antidiabetic agents the need for self monitoring of blood glucose was somehow negated.

The stand-alone statement that 'SMBG is not needed in order to adjust the dose of liraglutide' was inconsistent with the SPC with regard to the need for SMBG when combining treatment with a sulphonylurea. Further, the statement that 'Therefore, initiating liraglutide before a treatment that does require SMBG will have a favourable cost implication' seemed to ignore the fact that the majority of patients would already be on treatments that required SMBG when Victoza was started; the latter reflected the real-life clinical situation where Victoza was an add-on treatment to metformin and/or sulphonylurea, not vice-versa as was misleadingly implied by Novo Nordisk.

Section 3.8 discussed the numbers needed to treat (NNT) associated with liraglutide and invited a comparison with other antidiabetic agents as depicted in Figure 3.5. The calculation of the liraglutide NNT involves employing a composite endpoint which included reduction in SBP and no weight gain. Liraglutide was not licensed to reduce systolic blood pressure or weight and as such the NNT of 'four' was derived on a false premise; this was misleading and inconsistent with the liraglutide SPC.

For the reasons outlined above Lilly alleged that these four Sections were in breach of Clauses 2, 3.2, 7.2, 7.3, 7.4, 7.8, 7.9, 7.10, 8.1, 9.1 and 10.2 of the Code.

**RESPONSE**

Section 3.1: Novo Nordisk submitted that the value of any antihyperglycaemic agent both from a clinical and cost-effectiveness perspective could only be evaluated properly if effects and side-effects or elimination of side-effects were all considered. Thus mentioning the additional benefits of no weight gain, and systolic blood pressure provided a full evaluation and was as such, acceptable. Novo Nordisk did not agree that this section would imply that liraglutide had licensed indications other than that of improving glycaemic control.

Section 3.6: Novo Nordisk submitted that it did not believe the statement that liraglutide could be used at any time of day was misleading. It was consistent with Section 4.2 of the Victoza SPC.

Novo Nordisk disagreed that the statement 'SMBG is not needed in order to adjust the dose of liraglutide' was inconsistent with the liraglutide SPC. Novo Nordisk was unclear as to the allegation that 'The reader was invited to consider the cost advantage conferred by Victoza in that, when it was combined with oral antidiabetic agents the need for SMBG was somehow negated'. It failed to see how this could be the interpretation of this clause. The only mention of oral antidiabetic agents was where it stated that 'oral medication has not been factored

into the cost-effective analysis' and where examples of the number of SMBG tests were recommended, where SMBG tests were clearly recommended.

Novo Nordisk disagreed with Lilly's allegation that the statement 'initiating liraglutide before a treatment that does require SMBG will have a favourable cost implication' was misleading as it did not reflect the true clinical situation. The purpose of this statement was to simply confirm, in the cost effectiveness analysis that if liraglutide **were to be** initiated before a treatment that required SMBG, there would be a cost benefit. It was a hypothetical analysis, and as such, not misleading.

Section 3.8: As to the allegation concerning weight reduction, Novo Nordisk referred to its response in point D2 above to Sections 2.1, and 2.5.2, and 2.5.3 of Section 2 and its response in relation to points B3 and B4 above.

**PANEL RULING**

The Panel noted from Novo Nordisk's submission that mentioning the additional benefits of no weight gain and systolic blood pressure provided a full evaluation and was acceptable. The Panel noted that Section 3.1 included the claims that liraglutide was 'cost-effective compared with glimepiride when added to metformin monotherapy (cost/QALY £23,598), and with rosiglitazone when added to glimepiride monotherapy (cost/QALY £10,751)'. The basis for these calculations was given in Tables 3.2 and 3.3. The clinical inputs 'Change in HbA1c', 'Change in SBP' and 'Change in BMI' were listed in each table. Table 3.2 was based on a sub group of patients from Nauck *et al* (LEAD 2). The BMI data was not given in Nauck *et al* (LEAD 2). The Panel noted the comments it had made about Nauck *et al* (LEAD 2) in Point B1 above.

Table 3.3 was based on a sub group of patients from LEAD 1.

The Panel considered that Tables 3.2 and 3.3 implied that the indications for Victoza included decreasing weight and systolic blood pressure. This was not so. Section 3.1 of the formulary pack did not make the licensed indication clear nor the magnitude of the weight reduction and blood pressure data. The material was incomplete thus misleading as alleged and a breach of Clauses 7.2 and 7.3 was ruled. These rulings were appealed.

The Panel considered that, in the context of a health economic evaluation, Section 3.6 was not misleading with regard to the administration of Victoza. In the Panel's view the important consideration was the once-daily administration of Victoza. That the SPC further advised that it had to be administered at about the same, convenient time each day was not important in terms of an economic evaluation. No breach of Clauses 3.2 and 7.2 was ruled.

Section 3.6 stated that the cost of self monitoring of blood glucose was added where necessary. It also stated that 'SMBG is not needed in order to adjust the dose of liraglutide. Therefore initiating liraglutide before a treatment that does require SMBG will have a favourable cost implication'. The Panel noted Lilly's view that the statement appeared to ignore the fact that when Victoza was started the majority of patients would already be on treatments that required SMBG. The section implied that liraglutide would be used prior to a sulphonylurea. The Panel considered that there might be a theoretical cost benefit but this was not made clear. A breach of Clause 7.2 was ruled.

Section 3.8 'Number needed to treat one patient successfully to target' included results from a meta-analysis comparing patients treated to <7.0% HbA1c, <130mmHg SBP with no weight gain. The Panel noted that the composite endpoint had been made clear and was relevant to diabetic patients. The SPC included data for changes in weight and blood pressure. It would have been interesting to include the data purely for the licensed indication ie reduction in HbA1c. The Panel considered that this section was not misleading with regard to the licensed indication as alleged. No breach of Clauses 3.2 and 7.2 was ruled.

The Panel noted that Lilly had alleged a breach of Clauses 7.8 and 10.2 of the Code without giving any details of what was the subject of the allegations. In the circumstances the Panel considered that insufficient detail had been provided by Lilly and thus no breach of Clauses 7.8 and 10.2 was ruled.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. This ruling was appealed. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use.

**APPEAL BY NOVO NORDISK**

Novo Nordisk submitted that Section 3 was focused on the health economy of Victoza. In order to evaluate the cost-effectiveness of a medicine the applied model should consider changes in the clinically relevant parameters triggered by the medicine. The decision whether a compound was cost-effective in type 2 diabetes did not depend purely on its efficacy (ie improving HbA1c) but also on the additional benefits that the medicine could provide. Tables 3.2 and 3.3 listed the components of the health economy model. In this context, the tables did not imply the indication of a medicine, but the clinically relevant components of the model on the basis of which different stakeholders could make decisions about cost-effectiveness. Novo Nordisk submitted that the relevant target group of the formulary pack (such as budget holders) would not draw conclusions from the components of a health economy model in terms of the licensed indication of the medicine. Furthermore, it was reasonable to assume that they also read the

clinical summary of Victoza (Section 2) which clearly stated the licensed indication of the product (as discussed in point D2 above).

On the basis of the above Novo Nordisk did not agree with the Panel that Tables 3.2 and 3.3 were in breach of Clauses 7.2 and 7.3 of the Code.

Novo Nordisk submitted that as it had appealed all but one of the breaches ruled by the Panel, it did not agree that high standards had not been maintained and it therefore appealed the Panel's ruling in this regard.

**APPEAL BOARD RULING**

The Appeal Board noted that Section 3 was a 'Health Economic Evaluation'. The comparisons in Tables 3.2 and 3.3 were consistent with a health economic evaluation which would look at all of the benefits of the medicine including in this instance changes in weight and systolic blood pressure. The Appeal Board considered that Tables 3.2 and 3.3 did not mislead as to the indications for Victoza they reflected the relevant factors about its cost effectiveness. No breach of Clauses 7.2 and 7.3 was ruled. The appeal on this point was successful.

The Appeal Board noted all the rulings regarding Section 3 of the formulary pack and did not consider that Novo Nordisk had failed to maintain high standards. The Appeal Board ruled no breach of Clause 9.1. The appeal on this point was successful.

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At the completion of its consideration of this case, the Appeal Board was concerned about the presentation of the complaint. The Appeal Board deplored the way the complaint had been constructed with so many repetitive allegations. The response to the complaint could also have been better constructed; however some of the problems were as a direct result of the nature of the complaint. The time taken by the Panel and the Appeal Board to consider this case could have been substantially reduced if the complaint had been better presented.

**Complaint received** **9 October 2009**

**Case completed** **28 April 2010**