CASE AUTH/2234/5/09

LILLY v NOVO NORDISK

Promotion of Victoza prior to the grant of its marketing authorization

Lilly alleged that, despite being recently ruled in breach of the Code for promoting Victoza (liraglutide) prior to the grant of a marketing authorization (Case AUTH/2202/1/09), Novo Nordisk continued to so promote Victoza. 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.

Novo Nordisk advised that Victoza had been granted a marketing authorization on 30 June 2009.

The detailed response from Novo Nordisk is given below.

Lilly alleged that an online educational resource sponsored by Novo Nordisk involved the pre-licence discussion and promotion of liraglutide. Lilly noted that a screen which it accessed in April 2009 stated 'Thank you for registering with Liraglutide online!' and appeared when the 'New User Registration' hyperlink was activated.

In inter-company correspondence, Novo Nordisk stated that this was an 'oversight' and that 'measures will be implemented as soon as possible', instead of immediately, to address this. Lilly refuted the suggestion that this was an unintentional error; 'Thank you for registering with Liraglutide online!' clearly demonstrated Novo Nordisk's intent to use the training module for pre-licence promotion of liraglutide. The removal of this wording did not negate Lilly's allegation.

Lilly cited a number of examples throughout the online resource in support of its allegations that promoted liraglutide prior to the grant of its marketing authorization and misleadingly compared liraglutide with its product Byetta which, unlike liraglutide, was licensed. Lilly further alleged that some of the comparisons had disparaged Byetta. Lilly's detailed allegations are given below. Lilly further noted that it was only at the end of Section 4.2.1 titled 'Overview' that the statement 'Liraglutide is not yet licensed in the UK' appeared in very small font such that it was almost obscured. Lilly alleged that this did not however mitigate the substantive issue in question.

Lilly also noted that the availability of this website was highlighted in the 'Resources and Support' section of Prescriber, 5 March 2009. Lilly alleged that promoting the availability of the website to the medical press effectively also supported the pre-licence promotion of liraglutide.

Lilly alleged that this activity constituted the pre-licence promotion of liraglutide, it invited misleading claims and comparisons with licensed medicines and represented the disguised promotion of liraglutide. Lilly alleged breaches of the Code including a breach of Clause 2.

The Panel was extremely concerned to see that following registration a message 'Thank you for registering with Liraglutide online!' appeared. This was compounded by the name of the website 'Realising the promise of the GLP-1 receptor.' The Panel considered that the first impression was not of an educational online resource but promotion of liraglutide as alleged. The Panel noted that Novo Nordisk had removed the reference to liraglutide.

Overall the Panel was extremely concerned about the material in question. It included detailed information about liraglutide, a product that did not have a marketing authorization. The Panel considered that the material promoted liraglutide. In this regard the Panel noted the initial references to exenatide and the failure to be very clear about the differences in the regulatory status of the products. A breach of the Code was ruled. The material was misleading and included misleading comparisons. Breaches of the Code were ruled. The Panel ruled a breach of the Code in relation to a section on tolerability and safety. The Panel did not consider the material disparaged Byetta and no breach of the Code was ruled. The material was disguised promotion and a breach of the Code was ruled. High standards had not been maintained and a breach of the Code was ruled.

The Panel noted that promoting a medicine prior to the grant of the marketing authorization was an activity likely to be in breach of Clause 2. That clause was used as a sign of the particular censure. The Panel ruled a breach of Clause 2.

The front cover of the Sponsored supplement in The British Journal of Diabetes & Vascular Disease, November/December 2008, Volume 8 Supplement 2, 'The Modulating Effects of GLP-1 in Type 2 Diabetes: Proceedings from a symposium of the 43rd Annual Meeting of the European Association for the Study of Diabetes [EASD] Amsterdam, The Netherlands, 17 September 2007' stated 'This supplement has been supported by an educational grant from Novo Nordisk'. Lilly alleged that the supplement was being used promotionally by Novo Nordisk as evidenced by its distribution in the UK with The British Journal of Diabetes & Vascular Disease, January/February 2009, Volume 9 Issue 1.

Lilly alleged that the title and reference to the

EASD Annual Meeting misleadingly implied that the supplement was independent. This was further compounded by the format and layout of the supplement which suggested it was a part of and integral to the accompanying medical journal. The statement 'This supplement has been supported by an educational grant from Novo Nordisk' on the cover disguised the promotional nature of the material, which was in fact a paid for insert, editorially controlled by Novo Nordisk, detailing the proceedings of the company's sponsored satellite symposium which involved the pre-licence promotion of liraglutide.

The author, and chair of the satellite symposium introduced the five articles and stated 'Agents such as the GLP-1 receptor agonist exenatide and the DPP-4 inhibitors sitagliptin and vildagliptin are now available (the latter not in the USA) for utilisation in regimens to treat type 2 diabetes, while the GLP analogue liraglutide may soon be available'. Lilly alleged that the unlicensed status of liraglutide was not clearly stated and that its availability was underplayed relative to the wording adopted for vildagliptin. Lilly noted that it was only here that the derivation of four of the five articles was explained, albeit briefly, and linked to '… a symposium held on 17 September 2007, during the European Association for the study of Diabetes Meeting in Amsterdam'; although Novo Nordisk's sponsorship was omitted.

Lilly cited a number of examples with regard to the alleged promotion of liraglutide prior to the grant of its marketing authorization.

Lilly also alleged that a common theme in this insert was to misleadingly associate the discussion of liraglutide alongside licensed treatments such as Byetta thus creating the misleading impression that liraglutide should be regarded in the same context as Byetta, a licensed treatment.

Lilly noted liraglutide's unlicensed status and alleged that a discussion about its long-term effects on progression of type 2 diabetes (remarkable for a medicine that was not yet licensed!), clearly invited the suggestion that liraglutide was clinically relevant in the treatment of type 2 diabetes and available. This impression was reinforced in a 'Key messages' box which reiterated the messages that 'Liraglutide is a once-daily GLP-1 analogue that has a promising clinical profile including substantial improvement in glycaemic control without a risk for hypoglycaemia, and weight loss as an added benefit'.

Lilly alleged that an article 'Mechanisms behind GLP-1 induced weight loss' invited a discussion of liraglutide data and its effect on weight loss, and by reference to licensed medicines such as exenatide and sitagliptin invited the reader to consider it as 'a desirable option for the treatment of type 2 diabetes, as [it] improves[s] glycaemic control, improve[s] pancreatic function and induce[s] clinically meaningful weight loss' and its '…potential to modify type 2 diabetes disease progression'.

Lilly noted that although this article was not from the Novo Nordisk satellite symposium it involved editorial input from a Novo Nordisk employee as evidenced by the 'Acknowledgements' which stated 'The author has received many helpful comments to the manuscript from [a named doctor] ...'; this being a senior specialist from Novo Nordisk.

In conclusion, Lilly alleged that presenting the output of a Novo Nordisk run meeting as an independent supplement to a journal demonstrated poor knowledge of the Code. Health professionals generally looked to medical journals as a source of independent information therefore Novo Nordisk should have made it clear that the authors wrote the articles on behalf of and as a result of its promotional activities. Lilly alleged that the misleading description and presentation of this insert and its pre-licence promotion of liraglutide represented a breach of the Code.

Lilly alleged that this activity constituted the pre-licence promotion of liraglutide, it invited misleading claims and comparisons with licensed medicines and represented the disguised promotion of liraglutide in breach of the Code including Clause 2.

The Panel noted that the supplement had been initiated by Novo Nordisk and its agency. The authors were mostly those who had taken part in the company sponsored symposium.

The Panel considered that Novo Nordisk was inextricably linked to the production of the supplement. There was no arm's length arrangement between the provision of the sponsorship and the generation of the supplement. Circulation was not limited to those who attended the Novo Nordisk sponsored meeting as it was circulated with The British Journal of Diabetes and Vascular Disease in the UK. The Panel noted that it was an established principle under the Code that UK companies were responsible for the activities of overseas affiliates that came within the scope of the Code. Thus Novo Nordisk UK was responsible under the Code for the distribution in the UK.

Given the company's involvement and the content of the supplement, the Panel considered that the supplement was, in effect, promotional material for liraglutide. The Panel considered that the material was a paid-for insert from Novo Nordisk, not a supplement from The British Journal of Diabetes and Vascular Disease for which the journal's editorial board would have been responsible. The insert was distributed with The British Journal of Diabetes and Vascular Disease when liraglutide did not have a UK marketing authorization. The Panel considered that the insert promoted liraglutide to UK health professionals prior to the grant of its marketing authorization. A breach of the Code was ruled.

The insert misleadingly implied that liraglutide was licensed which was not so. A breach of the Code was ruled. The insert also invited the reader to make misleading comparisons about the licensed status of GLP-1-based therapies as alleged. A breach of the Code was ruled. The insert implied that it was a report of an independent meeting. The Panel considered that the insert was disguised promotion and a breach of the Code was ruled. The Panel considered that the role of Novo Nordisk was not clear. It was misleading to merely state that the insert had been supported by an educational grant from Novo Nordisk when the meeting was a Novo Nordisk sponsored symposium. The Panel considered that high standards had not been maintained and a breach of the Code was ruled.

The Panel considered that presenting the output of a Novo Nordisk meeting as an independent supplement to a journal demonstrated apparent poor knowledge of the Code. Health professionals generally looked to medical journals as a source of independent information; where authors wrote on behalf of pharmaceutical companies this must be clear. In the Panel's view the majority of readers would have viewed the material at issue quite differently if they had known that it was the report of a company sponsored meeting. The Panel considered that the description and presentation of the insert was such as to reduce confidence in, and bring discredit upon the pharmaceutical industry. A breach of Clause 2 was ruled.

Lilly stated that a promotional Symposium on Diabetes Care, March 2009, sponsored by Novo Nordisk, concluded with a 'Key Note Lecture' which was chaired by a senior clinical nurse specialist and included a one hour lecture/presentation 'A New Molecule in Diabetes – From Conception to Reality' delivered by a senior specialist, Novo Nordisk.

Lilly alleged that from this presentation it appeared that Novo Nordisk had intentionally commercialised liraglutide by a keynote lecture to promote the product and misleadingly imply that it was a licensed and relevant treatment option for the management of diabetes. This was evidenced by the context in which this particular lecture was presented ie preceded by an extensive discussion of subjects such as 'Diabetes – A Weighty Issue, New Treatments, Guidelines for Diabetes Care'.

Lilly alleged that this activity again constituted the pre-licence promotion of liraglutide, it invited misleading claims and comparisons with licensed medicines and represented the disguised promotion of liraglutide in breach of the Code including Clause 2.

The Panel noted that Novo Nordisk was responsible for the meeting. The title of the final presentation 'A New Molecule in Diabetes – From Conception to Reality' implied that the new molecule (liraglutide) was available for use which was not so. No details had been provided about the delegates. The Panel noted that the content referred to GLP-1 and its clinical potential as well as GLP-1 analogues. It included detailed information about liraglutide. The presentation compared liraglutide with exenatide, vildagliptin, glimepiride, rosiglitazone and glargine. The last few slides compared liraglutide and exenatide in relation to HbA_{1c}, HOMA, body weight and frequency of nausea. Each parameter favoured liraglutide and the HbA_{1c} and HOMA data were statistically significant. The final slide showed advantages for exenatide compared with glargine in relation to a composite endpoint of $HbA_{1c} \leq 7.4\%$ and weight gain $\leq$ 1kg. There did not appear to be any mention of the licensed status of the product. The final slide concluded that GLP-1 based therapies were highly interesting for treatment for type 2 diabetes and that GLP analogues might be made once daily treatments.

The Panel considered that the presentation promoted liraglutide when it did not have a marketing authorization. Thus the Panel ruled a breach of the Code as alleged. The title of the presentation was misleading and a breach of the Code was ruled. The presentation included comparisons with licensed medicines and could be seen as taking unfair advantage of the reputation of licensed medicines; thus a breach of the Code was ruled. The Panel did not consider that the meeting constituted the disguised promotion of liraglutide. The presentation was clearly promotional and no breach of the Code was ruled.

The Panel considered that high standards had not been maintained and ruled a breach of the Code. The Panel noted that promoting a medicine prior to the grant of the marketing authorization was an activity likely to be in breach of Clause 2. That clause was used as a sign of particular censure. The Panel ruled a breach of Clause 2.

Lilly noted that Novo Nordisk, together with an endocrine and diabetes society, was developing a local research strategy involving collaboration between centres in that area. To support this, a senior member of Novo Nordisk's sales department helped convene/facilitate the meeting, February 2009 which included discussion of liraglutide data in diabetes and obesity, the latest Levemir (insulin detemir) data, ongoing development/research projects and opportunities for collaboration in areas of pharmacological research in the local area amongst other things. Novo Nordisk extended an open invitation for any health professionals interested in participating in collaborative research projects to attend.

Lilly alleged that this was clearly a promotional meeting sponsored by Novo Nordisk as evidenced by the tacit and direct involvement of sales and marketing staff; this was acknowledged by Novo Nordisk in inter-company correspondence. Lilly queried why a member of the sales department would be involved in a meeting purporting to be focused on the information needs of 'potential and existing investigators' and where the objective was

'to update [delegates] on current and future research projects'.

Lilly alleged that the discussion of liraglutide data and other medicine development/research projects and data constituted pre-licence disguised promotion of liraglutide in breach of the Code including Clause 2.

The Panel noted that few details had been provided about this meeting. A presentation about 'On going development projects' had been given. The meeting appeared to have been held in response to an unsolicited request from the society for an update on ongoing and future research projects. From the agenda all of the speakers were from Novo Nordisk. The Panel was concerned that a senior member of the company's sales department had attended, albeit by invitation. The impression that that gave was important.

The Panel examined the slides used by Novo Nordisk for the presentation 'On going development projects'. The introduction referred to insulin research and development including future insulins and products Novo Nordisk was working on. It also referred to GLP-1 development. Information was presented about a study on islet transplantation which ran from April 2009.

The Panel was concerned that based on Novo Nordisk's activities already considered above, it was possible that liraglutide had been promoted to the audience. The Panel considered that this meeting appeared to be different to the one at issue above in that it was organised by Novo Nordisk in response to a request that the meeting be held. However the complainant had the burden of proving their complaint on the balance of probabilities. The Panel considered that given all the circumstances and the limited evidence before the Panel, the meeting could be regarded as the legitimate exchange of scientific information. Delegates were invited as potential or existing investigators, not as prescribers per se. No breach of the Code was ruled including Clause 2.

Lilly alleged that a promotional diabetes network meeting in March 2009 sponsored by Novo Nordisk invited presentations and discussions about the management of type 2 diabetes and presented information and various data about liraglutide, which, at the time, was unlicensed in the UK. A significant part of the meeting was devoted to a debate 'This house believes that GLP-1 agonists (such as exenatide and liraglutide) are the best second line therapy for type 2 diabetes'. Lilly alleged that the debate involved the presentation of liraglutide data to health professionals and engaged the audience in the pre-licence discussion of liraglutide and its place in the management of type 2 diabetes alongside licensed GLP-1-based therapies such as Byetta; this misleadingly implied that liraglutide was a licensed and relevant treatment option for the management of diabetes. The meeting was attended by Novo Nordisk sales representatives, which further exemplified the promotional nature of this meeting.

Lilly alleged that reference to topics on new treatment options in diabetes, the incretin system, modulators or mimetics of GLP-1, GLP-1 receptor agonists and the dipeptidyl IV receptor antagonists, stimulated a discussion on the availability of new treatments such as liraglutide thereby promoting the medicine prior to the grant of the marketing authorization. Lilly queried Novo Nordisk's assertion that only its regional medical advisor remained during the debate; this was contrary to the observations of Lilly staff who also attended.

Lilly alleged that this activity constituted the pre-licence promotion of liraglutide, it invited misleading claims and comparisons with licensed medicines and constituted the disguised promotion of liraglutide. As such it was in breach of the Code including Clause 2.

The Panel was concerned about the arrangements for the meeting. Novo Nordisk knew about the agenda about a month before the meeting. The topic of the debate that agents such as exenatide and liraglutide were the best second line therapy for type 2 diabetes was of concern given that one product had a marketing authorization and the other did not but was about to be so authorized. The title of the debate implied that both products were licensed which was not so.

The Panel noted that Novo Nordisk had denied the allegation that its sales representatives were present during the debate; Novo Nordisk submitted that only its local regional medical advisor was present. The Panel was concerned, given the title of the debate, that the regional medical advisor had attended even though Novo Nordisk submitted it had a clear lack of involvement in the debate. The Panel had similar concerns to those mentioned above. Novo Nordisk stated that the speakers were ultimately chosen by the main organiser of the meeting. There was no evidence before the Panel about the extent to which, if at all, Novo Nordisk had been able to influence or comment upon speaker selection. However Novo Nordisk had no involvement in the slide selection or topics for discussion. The Panel did not consider that Novo Nordisk's payment for an exhibition stand at the meeting meant that Novo Nordisk had sponsored the meeting and was responsible for its content. The Panel noted its concerns about the title of the debate and Novo Nordisk's knowledge thereof. However, on the evidence before it, the Panel decided that Novo Nordisk was not responsible for content of this meeting and thus no breaches of the Code were ruled including Clause 2.

The annual conference of a diabetes managed clinical network conference, April 2009 discussed various diabetes related topics by way of formal presentations and workshops and included a workshop focussing on the incretin mimetics. Lilly alleged that although this meeting was facilitated

by Novo Nordisk its sponsorship was not declared on the conference agenda. Novo Nordisk also had a promotional stand at the meeting; three of its sales representatives together with the sales manager attended the presentations and workshops which discussed incretin mimetics.

Lilly noted that in inter-company correspondence Novo Nordisk acknowledged that it 'helped fund the travel expenses of a visiting professor' and it also did not declare sponsorship of the meeting materials. This was attributed to error and the medical department not being told about the meeting.

Whilst the latter explanation offered no mitigation, Lilly queried Novo Nordisk's assertion that the professor was invited by the diabetes managed clinical network independently of Novo Nordisk. Lilly had it on good authority that the professor's input was facilitated by Novo Nordisk and that this included payment of an honorarium. This could be disclosed should it be required.

Lilly alleged that the professor's presentation 'Emerging New therapies in Diabetes Care' involved an unbalanced discussion of Byetta and liraglutide and invited a comparison of the two. In particular, reference was made to unpublished data from Novo Nordisk's Lead 6 study, a head-to-head comparison of Byetta and liraglutide. There was no clear indication of the licensed status of liraglutide and the impression created, by association to Byetta, was that liraglutide was available and a clinically relevant treatment option.

Lilly was also disappointed that both the speaker and Novo Nordisk disparaged Byetta throughout the presentation by referring to it as 'lizard spit'. Further, the discussion of Byetta was unbalanced and relatively abbreviated compared with that on liraglutide. To compound matters the speaker also stated that Byetta was only 50% homologous in comparison to human (physiological) GLP-1; although factually correct, the context in which this was discussed implied an inferior efficacy of Byetta. The speaker also inferred that liraglutide was developed later than Byetta because Novo Nordisk had deliberately taken longer researching this medicine in a more scientific way and hence liraglutide 97% homologous with human GLP-1; the implication being that Lilly had not conducted proper scientific research leading to the development of inferior products such as Byetta.

This presentation and the attendant workshop represented the pre-licence and disguised promotion of liraglutide which was further illustrated by the discussion of data comparing reduction of HbA_{1c} and weight loss data for Byetta and liraglutide. This was misleading as it implied, by association to Byetta, a licensed product, that liraglutide was also available and clinically relevant.

This activity constituted the pre-licence promotion of liraglutide, it invited misleading claims and comparisons with licensed medicines and constituted the disguised promotion of liraglutide. Lilly alleged breaches of the Code including Clause 2.

Lilly alleged that it was evident that Case AUTH/2202/1/09 did not represent an isolated instance of the pre-licence promotion of liraglutide by Novo Nordisk but was part of a concerted commercially driven objective. The above examples clearly demonstrated that Novo Nordisk had consistently, intentionally and widely promoted the availability of liraglutide in the UK prior to the grant of a marketing authorization. It was also evident that Novo Nordisk's medical and sales departments had not enforced the necessary standards with regard to compliance with the Code and also, on the company's own admittance, its internal policies and procedures.

In response to a request for further information Lilly stated that the undisclosed information it had regarding the honorarium paid to the professor was obtained from a managed care network which verbally confirmed that it had been paid £800 by Novo Nordisk to cover the professor's honorarium as a speaker. The managed care network then paid the professor.

Further, Lilly alleged that a Novo Nordisk sales representative transported the professor from the airport to the meeting and then on to another meeting; this was at odds with Novo Nordisk's position that the diabetes managed clinical network selected and invited the speaker entirely independently of the company.

The Panel noted that the professor's presentation included background information about GLP-1. A slide of a Gila Monster lizard was included and another slide headed 'GLP-1 analogues-available/in development' stated that Byetta came from Gila saliva. The next product mentioned on this slide was liraglutide with details that it was once daily. There was no distinction as to which medicines had marketing authorizations and which did not. Similarly a slide headed 'Efficacy of incretin therapeutics' unfavourably compared HbA_{1c} and body weight loss for Byetta with that for liraglutide and included FPG decreases and HbA_{1c} reductions for Januvia (sitagliptin) and Galvus (vildagliptin). The only product that did not have a marketing authorization was liraglutide and again no mention of this difference was made in the slides. Two other slides showed statistically significant advantages for liraglutide over exenatide in reduction of HbA_{1c} and improvement in beta-cell function over 26 weeks. The final slides referred to the pipeline for type 2 diabetes therapy.

The Panel was extremely concerned about the arrangements for Novo Nordisk's involvement in this meeting. It was not clear from Novo Nordisk's submission whether it had paid travel expenses only or paid an honorarium as alleged by Lilly. The role, if any of a Novo Nordisk representative in

providing/facilitating transport to and from the meeting was not clear. The agenda did not refer to Novo Nordisk's sponsorship of the professor. It was unacceptable for this not to be made clear on the documentation. In this regard the Panel considered that high standards had not been maintained and a breach of the Code was ruled.

The Panel noted Novo Nordisk's submission that the meeting was arranged by the diabetes managed clinical network which had selected and invited the speaker entirely independently of Novo Nordisk. However Novo Nordisk had contributed to the costs of the professor. Companies could not fund or otherwise facilitate a speaker as a means of avoiding the requirements of the Code. Given the title of the professor's presentation 'Emerging New Therapies in Diabetes Care' and the role of Novo Nordisk, it should have seen the materials prior to the presentation. The Panel was also concerned that Novo Nordisk was unsure as to where the professor had obtained Novo Nordisk unpublished material. Novo Nordisk should have checked the position with its head office.

Taking all the circumstances into account the Panel considered that, given Novo Nordisk's role, the sponsored presentation in effect promoted an unlicensed medicine. Thus a breach of the Code was ruled. This was disguised promotion and the material was misleading and included misleading comparisons. High standards had not been maintained. Breaches of the Code were ruled.

The Panel noted that Novo Nordisk had facilitated the professor's attendance and that he had somehow been given access to the company's unpublished data on file. The company's association with the speaker should have been made clear to the delegates. Novo Nordisk's omission in this regard reduced confidence in and brought discredit upon the industry. A breach of Clause 2 was ruled.

The Panel was extremely concerned that Novo Nordisk had promoted a medicine prior to the grant of its marketing authorization on a number of occasions. There appeared, in general, to be a poor understanding of the requirements of the Code. Novo Nordisk had acknowledged that its procedures were lacking; communication at all levels within the company was inadequate. The Panel considered that the circumstances warranted reporting Novo Nordisk to the Appeal Board for it to consider the matter in accordance with Paragraph 8.2 of the Constitution and Procedure.

The Appeal Board was extremely concerned about this case; the promotion of a medicine prior to the grant of its marketing authorization was a serious matter and displayed a poor understanding of the requirements of the Code. As well as being prohibited by the ABPI Code, it was also prohibited by the EFPIA Code on the Promotion of Prescription Only Medicines to, and Interactions with, Health Professionals. Headquarters staff in Denmark should know about the EFPIA Code. According to Novo Nordisk the website had been subjected to regulatory and legal review. The Appeal Board was not convinced that Novo Nordisk fully understood the seriousness of the matter and was especially concerned to note that the company had recently been found in breach of the Code for promoting liraglutide prior to the grant of its marketing authorization (Case AUTH/2202/1/09).

The Appeal Board noted that as a result of the rulings in this case Novo Nordisk had instigated a major review of its compliance systems, procedures and training. Code training of headquarters' staff was soon to be conducted by teleconference although the Appeal Board queried whether this was an effective training medium, given the seriousness of the case. The Appeal Board was very concerned about the apparent lack of influence that Novo Nordisk in the UK had over its headquarters in Denmark regarding compliance of material which came within the scope of the UK Code.

The Appeal Board decided in accordance with Paragraph 11.3 of the Constitution and Procedure to require an audit of Novo Nordisk's procedures in relation to the Code to be carried out by the Authority. The audit should be conducted as soon as possible. The Appeal Board suggested that relevant staff from Denmark should be interviewed. On receipt of the audit report the Appeal Board would consider whether further sanctions, including a report to the ABPI Board of Management, were necessary. In addition the Appeal Board decided that Novo Nordisk should be publicly reprimanded.

Upon receipt of the October 2009 audit report the Appeal Board was very concerned that as demonstrated in the audit reports of 2004/05 and the current audit report, Novo Nordisk clearly lacked processes to ensure compliance with the Code. This must be a priority for all including senior staff who must take more personal responsibility. The company must be able to show that this time it could change and develop attitudes and procedures which gave strong support to compliance.

The Appeal Board noted that Novo Nordisk was due to roll out a number of new standard operating procedures (SOPs) with training on them to commence early in 2010. This timeframe had been extended since the audit. The Appeal Board decided in accordance with Paragraph 11.3 of the Constitution and Procedure to require a further audit of Novo Nordisk's procedures in relation to the Code to be carried out by the Authority. The audit should be conducted in March 2010 when the Appeal Board expected Novo Nordisk's awareness of the Code and processes including the SOPs to be much improved and more embedded within the company. The re-audit in this case would take place at the same time as the audit required in Case AUTH/2269/9/09. On receipt of the audit report the Appeal Board would decide if further

sanctions were necessary.

Upon receipt of the March 2010 audit report the Appeal Board considered that Novo Nordisk's progress was not sufficiently rapid. It still had serious concerns about the company's approach and attitude to the Code. There were still significant problems with certification. Not all the standard operating procedures (SOPs) had been completed and trained out. This was now due to happen at the May sales conference (other than the SOP for medical and educational goods and services).

Overall, the Appeal Board considered that Novo Nordisk still did not appear to appreciate the seriousness of the situation. The Appeal Board considered requiring Novo Nordisk to submit material for pre-vetting as set out in Paragraph 11.3 of the Constitution and Procedure and/or report the company to the ABPI Board of Management. The Appeal Board decided to require another audit in June/July. On receipt of that audit report the Appeal Board would decide whether further sanctions, such as pre-vetting and/or a report to the ABPI Board were necessary.

Upon receipt of the July 2010 audit report the Appeal Board was concerned that it had taken some time but considered that significant progress had now been made. This must be maintained. The Appeal Board considered carefully all the options available noting that it had already decided that both cases (Cases AUTH/2234/5/09 and AUTH/2269/9/09) should be the subject of a public reprimand. It decided that no further action was necessary.

Eli Lilly and Company Limited alleged that Novo Nordisk Limited had promoted Victoza (liraglutide) prior to the grant of its marketing authorization.

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.

Lilly was disappointed that despite the recent ruling in relation to the pre-licence promotion of liraglutide (Case AUTH/2202/1/09), Novo Nordisk apparently continued to disregard both the spirit and tenet of the Code and engaged in the pre-licence promotion of liraglutide, as evidenced by a number of activities.

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Novo Nordisk advised that Victoza had been granted a marketing authorization on 30 June 2009.

Victoza was licensed to treat type 2 diabetes mellitus 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.

The items at issue were as follows.

1 Educational website – 'Realising the promise of the GLP-1 receptor'

Lilly wrote to Novo Nordisk and 20 November 2008, concerned about the pre-licence promotion of liraglutide in the online Training Module developed by Novo Nordisk entitled 'Latest Advances in the Treatment and Management of Type 2 Diabetes – The Incretins'. As Novo Nordisk agreed to remove reference to liraglutide from the training module, Lilly did not complain about this matter in Case AUTH/2202/1/09.

Lilly was therefore disappointed, that a similar educational resource sponsored by Novo Nordisk was currently available online and once again, in the guise of educational material, involved the pre-licence discussion and promotion of liraglutide.

COMPLAINT

Lilly alleged that the primary objective of this website was to facilitate the pre-licence promotion of liraglutide and noted that a screen which it accessed on 23 April 2009 stated 'Thank you for registering with Liraglutide online!' and appeared when the 'New User Registration' hyperlink was activated.

In inter-company correspondence, Novo Nordisk stated that the screen '... was quite clearly, an oversight' and that 'measures will be implemented as soon as possible', instead of immediately, to address this. Lilly refuted the suggestion that this was an unintentional error; the wording 'Thank you for registering with Liraglutide online!' clearly demonstrated Novo Nordisk's intent to use the training module as a platform upon which to base pre-licence promotion of liraglutide. The removal of this wording did not negate Lilly's allegation that this website constituted the pre-licence promotion of liraglutide.

Lilly alleged that Module 4 ('Anti-diabetic strategies based on the incretin hormone system'), (ref UK/LR/0508/0011) invited a broad range of discussion and comparison of the efficacy and safety of various treatment strategies, some of which were licensed and some in development, such as liraglutide, and therefore unlicensed.

Section 3 of Module 4 (ref UK/LR/0508/0011; 'Available treatment options for type 2 diabetes based on the incretin hormone system'), misled readers as they were not informed which treatments within the classes discussed were currently available/licensed; a previous reference to 'learning outcomes' suggested that the provision of

this type of important information would be implicit given the title of this particular section. Therefore, given that liraglutide featured prominently in this online resource, to omit early clarification of its unlicensed status misled readers not only by omission but also by association ie discussion of liraglutide alongside licensed treatments in the class such as Byetta.

Section 4.1 of Module 4 (ref UK/LR/0508/0011) presented, in brief, an 'Overview and therapeutic indications' of Byetta. It was correctly stated that exenatide was first approved for the treatment of type 2 diabetes in 2005 and was now available for this purpose in many countries around the world. However, Lilly alleged that it failed to clarify to the reader that exenatide was the only licensed and available GLP-1 receptor agonist; this omission was intentional and misled the reader regarding the place of liraglutide, as a treatment option which was discussed extensively in Module 4.

Section 4.2 of Module 4 (ref UK/LR/0508/0011) was titled 'Liraglutide' in large emboldened font and provided an extensive discussion of the efficacy of liraglutide and information about clinical trials with comparators including metformin. This was further elaborated and reiterated in the 'Knowledge Tests' associated with the module thereby further maximising the opportunity to promote liraglutide pre-licence.

Lilly noted that it was only at the end of Section 4.2.1 titled 'Overview' that the statement 'Liraglutide is not yet licensed in the UK' appeared in very small font such that it was almost obscured. Lilly alleged that this did not however mitigate the substantive issue in question, which was the provision of pre-licence information on liraglutide.

Importantly, Lilly alleged that the format and layout of Module 4 intentionally misled by implication and invited a direct and misleading comparison of liraglutide with Byetta.

Lilly alleged that the efficacy and clinical trials information presented for liraglutide effectively invited a comparison of the efficacy of liraglutide in relation to Byetta and its licensed indication; the implication invited was that it was fair, balanced and legitimate to promote a comparison of an unlicensed medicine with one that was. This comparison was not only unfair and inappropriate but was unbalanced in favour of liraglutide given the abbreviated nature of the Byetta section of the module in comparison with that detailing liraglutide information.

Lilly alleged that this was further highlighted in Section 4.2.2 ('Effects on blood glucose control') which discussed the 'Effectiveness of liraglutide versus placebo and comparator drugs'. Table 3 referred to comparative HbA_{1c} data from the Lead 2 and Lead 5 clinical studies. The reader was indirectly invited to also compare the HbA_{1c} values for Byetta provided earlier in the module; any such comparison of liraglutide with Byetta was not based on a direct head-to-head comparison and was therefore misleading, unfair and unsubstantiated.

Lilly alleged that comparisons with other GLP [glucagon – like peptide] -1R agonists in development were presented in Section 4.3 alongside the statement '…even those agents still in preclinical development will not be available for prescription at present or in the near future'. Interestingly, this statement was not applied to liraglutide despite its clear applicability and relevance. The wording intentionally invited a comparison with liraglutide and suggested that liraglutide was a more clinically relevant choice given its implied availability. Indeed, in inter-company correspondence Novo Nordisk appeared to validate the discussion of liraglutide alongside products in preclinical development because liraglutide 'is in clinical development, not preclinical development.' This clearly demonstrated Novo Nordisk's failure to understand that the pre-licence discussion of liraglutide in a promotional website was not acceptable regardless of the development stage of the medicine.

Lilly noted that Sections 7 and 7.1 (ref UK/LR/0508/0011) of Module 4 discussed the tolerability and safety considerations of GLP-1 receptor agonists. Lilly failed to comprehend the relevance of any safety consideration of an unlicensed medicine such as liraglutide particularly when it invited a comparison with the safety profile of Byetta and other licensed treatments. Lilly alleged that given the latter, of particular concern was the unbalanced, alarmist and disparaging nature of the information and claims made in support of the safety profile of liraglutide in comparison with Byetta. For example, the promotional tone of the statement 'liraglutide [like all GLP-2 receptor agonists] is also associated with an increased incidence of nausea and other gastrointestinal side effects relative to placebo. Again, however, these are usually mild, transient, and infrequently associated with treatment discontinuation.', was in stark contrast to those about safety issues related to Byetta treatment; the latter drew attention to ' ... a high incidence of hypoglycaemia ...', 'A review of 30 cases of acute pancreatitis in patients receiving exenatide led to the addition of information relating to the risk of pancreatitis to the precautions section of the prescribing information of this product in January 2008'. Why had Novo Nordisk not employed an equally rigorous approach to providing equally relevant details clarifying the licensed status of liraglutide?

Lilly alleged that the 'Self-assessment' section associated with Module 4 could have afforded the opportunity to address the latter glaring omission. Instead however, as evidenced by question 4, the assessment invited a consideration of the route of administration of liraglutide by asking the question 'GLP-1R agonists such as exenatide and liraglutide are peptides that are administered by ...'.

The latter invited the reader to be misled by implication, omission and association to Byetta that liraglutide was available and not unlicensed in the UK.

Lilly alleged that Module 3 ('The physiology of incretins') and its association with Module 4 of this website further exemplified the misleading and contrived promotion of the liraglutide safety profile by association and implication. Section 6.4 of the module (ref UK/LR/0508/0011; 'Blood glucose lowering by GLP-1 is safe and effective') discussed the safety of injecting GLP-1 infusions and stated that these were 'well tolerated' and 'The incidence of all-cause adverse events was similar for both the placebo'.

This was followed by Section 7 ('Implications for therapy') which stated that 'The clinical studies summarised previously show that administration of GLP-1 has the potential to normalise blood glucose in patients with type 2 diabetes. Finally, infusions of GLP-1 given over three periods of a few days to several months were well tolerated. These observations support the potential for using novel therapeutic agents that act via GLP-1 receptors as monotherapy or within oral antidiabetic combination regimens. However, the extremely short survival of biologically active GLP-1 in the plasma renders treatment with GLP-1 itself impractical. Alternative strategies that exploit the incretin hormone system to deliver antidiabetic therapy are now available. These will be discussed in Module 4'.

Lilly also noted that the availability of this website was highlighted in the 'Resources and Support' section of Prescriber, 5 March 2009. Given the points above, Lilly alleged that promoting the availability of the website to the medical press effectively also supported the pre-licence promotion of liraglutide.

Lilly categorically refuted Novo Nordisk's assertion that this website was simply an educational resource. This activity constituted the pre-licence promotion of liraglutide, it invited misleading claims and comparisons with licensed medicines and represented the disguised promotion of liraglutide. Lilly alleged breaches of Clauses 3.1, 7.2, 7.3, 7.9, 8.1 and 12.1 of the Code and, given the serious nature of the matter, a breach of Clauses 9.1 and 2.

RESPONSE

Novo Nordisk submitted that the website in question was authored by an external agency. It was initiated by Novo Nordisk UK as an educational resource for health professionals to raise their awareness of the GLP-1 receptor, together with current and future therapies based around incretins. The web pages were approved and certified in accordance with the Code. The Code allowed educational activities, and Novo Nordisk submitted that this website complied with the Code, and was a useful resource for health professionals.

Novo Nordisk agreed that the statement 'Thank you for registering with Liraglutide online!' on the registration hyperlink page was unacceptable from the perspective of the Code and could be perceived as leading to a platform where there was pre-licensed promotion of liraglutide, which was not the case, once the site was entered. It therefore instructed the external agency to promptly remove this statement from the web page, which it did within 24 hours. Novo Nordisk rejected other allegations in the complaint made by Lilly regarding the website.

Novo Nordisk noted that the four modules of the educational website extensively discussed the following:

pathogenesis of type 2 diabetes mellitus (focusing on ß-cell failure) (Module 1); the potential advantages/disadvantages of the available antihyperglycaemic compounds other than incretin-based therapies (Module 2);
the physiology of the incretin system (Module 3) and incretin-based therapies (Module 4).

Liraglutide was first and only mentioned in Module 4 therefore its licence status was sufficiently clarified in the Overview section of this Module; namely Section 4.2.1 – the first section mentioning the compound.

The amount of scientific information relating to type 2 diabetes in the modules relative to the amount of information about liraglutide showed the commitment to create an important educational tool for health professionals interested in this therapy area. Lilly suggested that liraglutide featured prominently in this online resource, but had been covered only in the sections where this was relevant, such as where exenatide was discussed. Thus this suggestion was refuted.

Lilly alleged that Section 3 could mislead the readers in terms of the licence status of liraglutide, however Novo Nordisk submitted that the section in the link 'Click here to view descriptions of the therapeutic options' solely described the two classes of incretin-based therapies (DPP-IV inhibitors and GLP-1R agonists) without specifically mentioning any compound. Liraglutide was mentioned first in Section 4.

Lilly also alleged that Section 4.1 failed to highlight the fact that exenatide was the only licensed and available GLP-1 receptor agonist and this would mislead the readers in terms of the licence status of liraglutide. Again, liraglutide was not mentioned in this online educational tool by this point; it was first discussed in the next section. Since the next overview section had the statement which clarified that liraglutide had currently no marketing authorization in the UK, Novo Nordisk submitted that the lack of emphasis of the issue raised by Lilly would not mislead the reader as suggested.

Novo Nordisk submitted that the allegation that the sentence which highlighted the licence status of liraglutide could only be found at the end of Section 4.2.1 was true, however Lilly had failed to note that this was the first section discussing this compound, and as such, Novo Nordisk submitted this was the relevant part of Module 4 in which to emphasise this fact. The statement was in the same font as the rest of this paragraph and could not, as stated, be considered as 'very small font such that it is almost obscured'.

Lilly stated that the whole format and layout of Module 4 invited a direct and misleading comparison of liraglutide with Byetta. Novo Nordisk submitted that such comparisons would not have any meaningful scientific grounding and health professionals were also aware of this. Therefore Lilly's allegation suggested that health professionals did not know how clinical trial results should be compared in a scientific way; this was discourteous to clinical colleagues.

Novo Nordisk submitted that it was important to highlight that the out of context emphasis in Lilly's complaint and the suggestion that Novo Nordisk had discussed exenatide and liraglutide in an unfair, unbalanced way was unsubstantiated when viewing the material to which it referred as a whole. Lilly had alleged that liraglutide featured prominently in Section 3 of this online resource. In fact only Module 4 discussed liraglutide and provided exactly the same amount of information about it as it did about exenatide. In regard to Section 4.1 Lilly had alleged that Byetta was presented in brief whereas liraglutide was discussed extensively. In fact the structure of the sections where these agents were discussed were the same, in that they each provided exactly the same amount of information for each compound. Although Lilly had alleged that Section 4.2 was titled 'Liraglutide' in large emboldened font; Section 4.1 about exenatide was titled in exactly the same way. Novo Nordisk noted that Lilly had alleged that this comparison was not only unfair and inappropriate but was unbalanced in favour of liraglutide given the abbreviated nature of the Byetta section of the module compared with to that detailing liraglutide. Novo Nordisk was particularly disappointed about this view given that the structure of Module 4 provided the same amount of information on each compound.

Novo Nordisk submitted that Lilly's concern relating to Section 7 was unclear how it failed to understand that it was possible to provide safety data about a compound in the pre-licence period. Fortunately regulatory authorities acknowledged safety data from clinical trial phases of a medicine development program, and acknowledged that these programs served as a solid basis for any new licence approval.

Regarding Lilly's concern that information and claims made in support of the safety profile of liraglutide in comparison with Byetta were unbalanced, alarmist and disparaging, Novo Nordisk submitted that the quoted hypoglycaemia incidence rates were in Byetta's prescribing information and came from the most important randomized clinical trials Lilly had conducted with exenatide in the late phase of its clinical development programme. It was unfortunate that Lilly considered facts from its own prescribing information were disparaging.

Furthermore Novo Nordisk submitted that it was difficult to comprehend the relevance of comparing the 'promotional tone' used, according to Lilly, in the statement supporting liraglutide in terms of its gastrointestinal side effects to the safety issues relating to the treatment with Byetta regarding its hypoglycaemic risk profile and the risk of pancreatitis, which resulted in Lilly requesting a label change by the FDA in the Byetta prescribing information.

Novo Nordisk submitted although liraglutide was discussed in a fair and balanced way compared to exenatide only in Module 4 interestingly Lilly also considered Module 3 misleading and promotional in terms of the safety profile of liraglutide. In fact this module was about the physiology of incretins in general without mentioning any specific medicine. With regard to Lilly's particular concern about Section 6.4, this provided information about the safety profile of GLP-1 based blood glucose lowering therapy and referred to two publications published in Diabetes Care in 2001 and 2003. Both papers investigated biosynthetic GLP-1, hence any interpretation of the results should be equally relevant both in terms of exenatide and liraglutide. Thus Novo Nordisk denied that this section could be considered as disguised promotion of liraglutide. Novo Nordisk intended this section to provide useful scientific information for health professionals only, rather than to promote any specific medicine.

Novo Nordisk provided, in confidence, the agreement between it and the external agency which developed the educational website. The agreement clearly showed the intention to develop an online tool for non-promotional educational purposes. Novo Nordisk noted that Schedule 1 of the agreement showed that it clearly understood how liraglutide could be discussed before and after its marketing authorization had been granted.

Finally Novo Nordisk stated that there were 109 registered users of this website on 8 June 2009. The low number certainly did not indicate a lack of interest in the topic, but rather reflected the fact that Novo Nordisk had not promoted the availability of this website, and that it was primarily used as a reference for those health professionals who, in an unsolicited approach to Novo Nordisk, requested more information about GLP-1 based therapies from its medical information team.

Given the above Novo Nordisk categorically refuted the allegations that the education website facilitated the pre-licence promotion of liraglutide.

However, since this was the second time Lilly had tried to challenge the value of this educational tool alleging its promotional nature, Novo Nordisk had decided to close the website although it still believed it was a valuable source of information for health professionals.

PANEL RULING

The Panel noted that, in its response to the Authority, Novo Nordisk had stated that it had decided to close the website at issue. Lilly had not been notified. The Director considered, however, that in the circumstances inter-company dialogue had not been successful. The Panel considered the case.

The Panel noted that the Code permitted certain activities prior to the grant of a marketing authorization. The supplementary information to Clause 3 stated that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited provided that any such information or activity did not constitute promotion prohibited under Clause 3 or any other clause.

In the Panel's view the closer the grant of the marketing authorization for a product the more difficult it was to argue that activities constituted the legitimate exchange of medical and scientific information during the development of a medicine and were not promotion. The marketing authorization for Victoza was granted on 30 June 2009.

The Panel noted Novo Nordisk's submission that the website was an educational resource and queried whether providing such material about a product and its therapeutic area a few months before the grant of its marketing authorization would ever be acceptable under the Code given that the definition of promotion was any activity undertaken by a pharmaceutical company, or with its authority, which promoted the prescription, supply, sale or administration of its medicines. Obviously the content of such material would be important.

The Panel considered it was irrelevant how many users had registered to use the website as was the amount of information about liraglutide relative to other information.

The Panel was extremely concerned to see that following registration a message 'Thank you for registering with Liraglutide online!' appeared. This was compounded by the name of the website 'Realising the promise of the GLP-1 receptor.' The Panel considered that the first impression was not of an educational online resource but promotion of liraglutide as alleged. The Panel noted that Novo Nordisk had removed the reference to liraglutide. It did not appear on the version of the educational module provided by Novo Nordisk to the Authority. Nevertheless the Panel considered that the fact that such a reference had been included at all was of serious concern.

The Panel considered that it was misleading as alleged not to have made it clear that exenatide was the only licensed GLP-1 receptor agonist.

The Panel also considered that Section 4.2 would lead readers to compare exenatide and liraglutide. The comparative data presented for liraglutide did not include direct comparisons with exenatide which was not the impression given by the claim 'liraglutide was at least as effective as the comparator treatments in these trials'.

The separation between exenatide and liraglutide from other GLP-1R agonists which were described as being included for completeness and 'However unlike exenatide even those agents still in preclinical development will not be available for prescription at present or in the near future' further reinforced the impression that both exenatide and liraglutide were available for prescription. This was misleading.

Module 4 included many claims for similarities between exenatide and liraglutide or advantages for liraglutide. The Panel considered that this further added to the promotional nature of the material.

Section 7 on tolerability and safety considerations compared the profiles of exenatide and liraglutide. It referred to additions to the Byetta summary of product characteristics (SPC) in January 2008 to include the risk of pancreatitis. Byetta had received its marketing authorization in November 2006. The Victoza SPC referred to the risk of pancreatitis with other GLP-1 analogues and the need to discontinue Victoza and other potentially suspect medicinal products. The failure to include any of this information in the module was of concern particularly as it was not made clear that liraglutide did not have a marketing authorization and the difference in available information given that there was more experience with exenatide.

The Panel noted that Lilly's concern that statements about the safety profile of liraglutide went beyond the inclusion of the hypoglycaemia incidence rates from the Byetta SPC as submitted by Novo Nordisk.

The agreement with the external agency made it clear that the material on the website needed to comply with the ABPI Code among other regulations and codes.

The Panel was extremely concerned about the material in question. It included detailed information about liraglutide, a product that did not have a marketing authorization. The Panel considered that the material promoted liraglutide. In this regard the Panel noted the initial references to exenatide and the failure to be very clear about the differences in the regulatory status of the products. A breach of Clause 3.1 was ruled. The material was misleading and included misleading comparisons.

Breaches of Clauses 7.2 and 7.3 were ruled. The Panel ruled a breach of Clause 7.9 in relation to the section on tolerability and safety. The Panel did not consider the material disparaged Byetta and no breach of Clause 8.1 was ruled. The material was disguised promotion and a breach of Clause 12.1 was ruled. High standards had not been maintained and a breach of Clause 9.1 was ruled.

The Panel noted that promoting a medicine prior to the grant of the marketing authorization was an activity that was listed in the supplementary information as an activity likely to be in breach of Clause 2 of the Code. That clause was used as a sign of the particular censure. The Panel ruled a breach of Clause 2.

2 Sponsored supplement in The British Journal of Diabetes & Vascular Disease, November/December 2008, Volume 8 Supplement 2

The front cover of the above supplement, 'The Modulating Effects of GLP-1 in Type 2 Diabetes: Proceedings from a symposium of the 43rd Annual Meeting of the European Association for the Study of Diabetes [EASD] Amsterdam, The Netherlands, 17 September 2007' stated 'This supplement has been supported by an educational grant from Novo Nordisk'. Lilly alleged that the supplement was being used promotionally by Novo Nordisk as evidenced by its distribution in the UK with The British Journal of Diabetes & Vascular Disease, January/February 2009, Volume 9 Issue 1.

COMPLAINT

Lilly alleged that the above title and reference of the 43rd Annual Meeting of the EASD misleadingly implied that the supplement was an independent report of the proceedings from this meeting and not in fact those from a closed promotional satellite symposium run by Novo Nordisk. This was further compounded by the format and layout of the supplement which suggested it was a part of and integral to the accompanying medical journal. The statement 'This supplement has been supported by an educational grant from Novo Nordisk' as it appeared on the cover disguised the promotional nature of the material, which was in fact a paid for insert detailing the proceedings of a company meeting which involved the pre-licence promotion of liraglutide. The concept of the insert and its content was clearly derived and editorially controlled by Novo Nordisk and represented the outputs from its satellite symposium.

On page S1, the author, who chaired the Novo Nordisk satellite symposium introduced the five articles and stated 'Agents such as the GLP-1 receptor agonist exenatide and the DPP-4 inhibitors sitagliptin and vildagliptin are now available (the latter not in the USA) for utilisation in regimens to treat type 2 diabetes, while the GLP analogue liraglutide may soon be available'.

Lilly alleged that the unlicensed status of liraglutide was not clearly stated and that its availability was underplayed relative to the wording adopted for vildagliptin. Lilly noted that it was only here that the derivation of four of the five articles was explained, albeit briefly, and linked to '… a symposium held on 17 September 2007, during the European Association for the study of Diabetes Meeting in Amsterdam'; although the fact that it was sponsored by Novo Nordisk was conveniently omitted.

Lilly noted that on pages S10 – S18 the article 'Pharmacology of GLP-1 based therapies' discussed liraglutide clinical trial data and stated that 'Liraglutide is a once-daily human GLP-1 analogue with high (97%) sequence identity'. Lilly alleged that this wording implied a licensed posology for liraglutide. The article went on to make pre-licence promotional claims in support of the pharmacokinetics, pharmacodynamics, mode of action and clinical efficacy of liraglutide and invited the reader to consider the 'clinically relevant reductions in HbA_{1c} compared to placebo, without hypoglycaemia and with weight loss of up to 3kg'. Again, the author highlighted the licence status of vildagliptin by stating 'DPP-4 inhibitors, such as vildagliptin (not available in the USA) ...' but failed to clarify that liraglutide was not licensed in the USA or in Europe; thus misleading by omission and suggesting, by association, that all the other GLP-1 based therapies mentioned were in fact licensed.

Lilly noted that on pages S19 – S25 the article 'Managing the ß-cell with GLP-1 in type 2 diabetes' discussed preclinical and clinical data in the pre-licence promotion of liraglutide for the treatment of type 2 diabetics.

Lilly alleged that a common theme in this insert was to misleadingly associate the discussion of liraglutide alongside licensed treatments such as Byetta. This was clearly demonstrated in a section entitled 'GLP-1 treatment in type 2 diabetes' where Byetta was discussed as 'The first GLP-1 analogue available …' This was then directly followed by the statement 'A second GLP-1 analogue is liraglutide. In the development of liraglutide ...' thus creating the misleading impression that liraglutide had already been developed and should be regarded in the same context as Byetta, a licensed treatment.

Given all of the above points Lilly alleged that the article on pages S26 – S33, 'Liraglutide, a once-daily human GLP-1 analogue' evidenced the significant extent to which liraglutide was discussed at the Novo Nordisk satellite symposium. Indeed, the article authored by the meeting chairman also made pre-licence promotional claims in support of the efficacy and safety of liraglutide. The abstract section stated 'The effects of liraglutide are maintained over 24h, allowing daily dosing. Liraglutide provides all of the beneficial actions of endogenous GLP-1: glucose dependant stimulation of insulin secretion, glucagon suppression, deceleration of gastric emptying, appetite

suppression/weight loss …', '... the risk of treatment-associated hypoglycaemia is low.', 'in clinical studies, liraglutide substantially lowered fasting and postprandial glucose concentrations, with an overall reduction in haemoglobin A_{1c} of up to 1-2%. In some studies liraglutide decreased several biomarkers of cardiovascular risk and lowered triglyceride levels significantly'.

Again, Lilly alleged that there was no explicit clarification that liraglutide was not licensed in the UK. Given the latter, the detailed discussion of liraglutide over the next six pages, which included the long-term effects of liraglutide on progression of type 2 diabetes (remarkable for a medicine that was not yet licensed!), clearly invited the suggestion that liraglutide was clinically relevant in the treatment of type 2 diabetes and available. This impression was reinforced in the 'Key messages' box which reiterated the messages that 'Liraglutide is a once-daily GLP-1 analogue that has a promising clinical profile including substantial improvement in glycaemic control without a risk for hypoglycaemia, and weight loss as an added benefit'.

Lilly alleged that on pages S34 – S41 an article 'Mechanisms behind GLP-1 induced weight loss' invited a discussion of liraglutide data and its effect on weight loss, and by reference to licensed medicines such as exenatide and sitagliptin invited the reader to consider it as 'a desirable option for the treatment of type 2 diabetes, as [it] improves[s] glycaemic control, improve[s] pancreatic function and induce[s] clinically meaningful weight loss' and its '…potential to modify type 2 diabetes disease progression'.

Lilly also noted that, unlike the preceding four articles, this one was not from the Novo Nordisk satellite symposium but did involve editorial input from a Novo Nordisk employee as evidenced by the 'Acknowledgements' which stated 'The author has received many helpful comments to the manuscript from [a named doctor] ...'; this being the same senior specialist from Novo Nordisk referred to in point 3 below.

In conclusion, Lilly alleged that presenting the output of a Novo Nordisk run meeting as an independent supplement to a journal demonstrated apparent poor knowledge of the requirements of the Code. Health professionals generally looked to medical journals as a source of independent information therefore Novo Nordisk should have made it clear that the authors wrote the articles on behalf of and as a result of its promotional activities.

Lilly alleged that the misleading description and presentation of this insert and its pre-licence promotion of liraglutide represented a breach of the Code.

Lilly did not accept the assertion that 'Due to the fact that Novo Nordisk had no input into this item, we do not feel able to comment on the specific issues raised in your letter'. The Novo Nordisk response during inter-company correspondence regarding this paid insert clearly acknowledged that both Novo Nordisk and its parent company disregarded the requirements of the Code with respect to promotional activities undertaken within the UK.

Lilly alleged that this activity constituted the pre-licence promotion of liraglutide, it invited misleading claims and comparisons with licensed medicines and represented the disguised promotion of liraglutide in breach of Clause 3.1, 7.2, 7.3, and 12.1 and, given the serious nature of the matter, breaches of Clauses 2 and 9.1.

RESPONSE

Novo Nordisk referred to inter-company dialogue in which it submitted that the supplement was initiated by its corporate offices in Denmark, in association with the USA affiliate. Within Novo Nordisk, there was a very clear standard operating procedure which stated that all material to be published in the UK, or for a UK audience, needed to be approved by the UK affiliate for Code compliance. Unfortunately, it appeared that the supplement in question was not sent to the UK for approval. Novo Nordisk was currently looking into re training its corporate offices and was taking steps to ensure that similar activities could not occur in the future.

Novo Nordisk submitted that Lilly was incorrect to claim that the supplement had been used promotionally. The supplement had not been issued directly to any health professional by any Novo Nordisk employee, had not been displayed on any promotional stand and had not been quoted from in any promotional material. In addition, Novo Nordisk had not used the supplement internally for training/education purposes.

Due to the fact that Novo Nordisk had no information about, and no input into the supplement in question it was unable to comment on the specific issues raised by Lilly.

In response to a request for further information Novo Nordisk confirmed that the supplement reflected the programme of a satellite symposium organised by Novo Nordisk in Amsterdam, September 2007, before the annual meeting of the EASD. However Novo Nordisk did not understand the concern regarding the layout of the supplement. This supplement was an official supplement to the British Journal of Diabetes & Vascular Disease, which was supported by a grant from Novo Nordisk (Novo Nordisk's funding role was highlighted on the front page of the journal). The fact that this was a paid supplement did not mean a different layout was required. In fact, such a supplement should be an integral part of the journal itself.

To Novo Nordisk's knowledge, save for the last paper, the content of the supplement was written by

the speakers of the symposium with no editorial input from Novo Nordisk. As was acknowledged by Lilly, the last paper was not derived from the symposium. It discussed GLP-1-induced weight loss from a general GLP-1 perspective and mentioned both exenatide and liraglutide in one single sentence respectively. The contribution by the Novo Nordisk's scientist was sufficiently emphasised in the acknowledgement at the end of the paper. Thus Novo Nordisk UK did not believe the last paper promoted liraglutide.

Novo Nordisk also did not believe Holst *et al* promoted liraglutide. This paper discussed the pharmacology of GLP-1-based therapies. The allegation that the paper discussed liraglutide clinical data and made pre-licence promotional claims was incorrect. In the main, the paper discussed the pharmacological effects of the native GLP-1 molecule (equally relevant from exenatide and liraglutide perspectives). The first paragraph on page S15 which was about a specific incretin-based compound rather than GLP-1 in general, actually discussed exenatide. In fact readers could find more clinical data in relation to trials on exenatide rather than clinical data relating to liraglutide. There was in fact only a small paragraph which mentioned liraglutide as one of the albumin-based GLP-1 analogues, in contrast to the remainder of this page which discussed Lilly's products (both licensed and unlicensed). The author also discussed exenatide LAR and provided comparable amounts of data about this future compound by Lilly as he provided about liraglutide. Novo Nordisk noted that the author explicitly stated that liraglutide was in the development phase ('Three compounds using different methods to achieve this are in development'). Furthermore Lilly referred to a quotation from the abstract 'clinically relevant reductions in haemoglobin A1c compared with placebo, without hypoglycaemia and with weight loss of up to 3kg', and donated this phrase as relating exclusively to liraglutide and hence a pre-licence promotional claim. However when this quotation was read in the context of the paper as a whole, it could be seen that the author actually related this statement to both exenatide and liraglutide.

The intention of the prominent authors of this whole supplement was to provide a useful educational source of balanced scientific information about GLP-1 based therapies. Novo Nordisk did not believe that when the supplement was read in its entirety that it would be considered as a promotional article in relation to liraglutide or at all.

However Novo Nordisk realised there was a failure in its internal review process relating to approval of this UK-based journal supplement by the UK affiliate. Its new legal and compliance team was currently addressing this issue with relevant colleagues from Novo Nordisk headquarters in Copenhagen in order to improve this internal procedure.

PANEL RULING

The Panel noted that it was acceptable for companies to sponsor material. It had previously been decided, in relation to material aimed at health professionals, that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the material in a manner favourable to its own interest. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its contents, but only if it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes.

The Panel noted that the objectives of the material in question, 'The Modulating Effects of GLP -1 in Type 2 Diabetes', was to provide the proceedings of a symposium, sponsored by Novo Nordisk at an international meeting, in the form of a journal supplement. The Panel considered that it would not always be possible to achieve this and comply with the requirements of the Code. Within the context of an international conference, attended by thought leaders, investigators and the like, it was possible for pharmaceutical companies to hold symposia about unlicensed products or indications as long as such activities were not otherwise promotional. The Code did not prohibit the legitimate exchange of medical and scientific information during the development of a medicine provided such activity was not promotion which was prohibited under Clause 3 or any other clause. The unsolicited distribution of symposia proceedings by a pharmaceutical company to health professionals who had not attended the meeting was not acceptable if the material referred to unlicensed medicines or did not otherwise comply with the Code.

The Panel noted that the supplement had been initiated by Novo Nordisk and its agency. The authors were mostly those who had taken part in the company sponsored symposium.

The Panel considered that Novo Nordisk was inextricably linked to the production of the supplement. There was no arm's length arrangement between the provision of the sponsorship and the generation of the supplement. Circulation was not limited to those who attended the Novo Nordisk sponsored meeting as it was circulated with The British Journal of Diabetes & Vascular Disease in the UK. The Panel noted that it was an established principle under the Code that UK companies were responsible for the activities of overseas affiliates that came within the scope of the Code. Thus Novo Nordisk UK was responsible under the Code for the distribution in the UK. Given the company's involvement and the content of the supplement, the Panel considered that the supplement was, in effect, promotional material for

liraglutide. The Panel considered that the material was a paid-for insert from Novo Nordisk, not a supplement from The British Journal of Diabetes & Vascular Disease for which the journal's editorial board would have been responsible. The insert was distributed with The British Journal of Diabetes & Vascular Disease when liraglutide did not have a UK marketing authorization. The Panel considered that the insert promoted liraglutide to UK health professionals prior to the grant of its marketing authorization. A breach of Clause 3.1 was ruled.

The insert gave the misleading impression that liraglutide was licensed and this was not so. A breach of Clause 7.2 was ruled. The insert also invited the reader to make misleading comparisons about the licensed status of GLP-1-based therapies as alleged. A breach of Clause 7.3 was ruled. The insert gave the impression that it was a report of an independent meeting. The Panel considered that the insert was disguised promotion and a breach of Clause 12.1 was ruled. The Panel considered that the role of Novo Nordisk was not clear. It was misleading to merely state that the insert had been supported by an educational grant from Novo Nordisk when the meeting was a Novo Nordisk sponsored symposium. The Panel considered that high standards had not been maintained and a breach of Clause 9.1 was ruled.

The Panel considered that presenting the output of a Novo Nordisk meeting as an independent supplement to a journal demonstrated apparent poor knowledge of the requirements of the Code. Health professionals generally looked to medical journals as a source of independent information; where authors wrote on behalf of pharmaceutical companies this must be clear. In the Panel's view the majority of readers would have viewed the material at issue quite differently if they had known that it was the report of a company sponsored meeting. The Panel considered that the description and presentation of the insert was such as to reduce confidence in, and bring discredit upon the pharmaceutical industry. A breach of Clause 2 was ruled.

3 Novo Nordisk Symposium on Diabetes Care, March 2009

Lilly stated that this promotional meeting, sponsored by Novo Nordisk, concluded with a 'Key Note Lecture' which was chaired by a senior clinical nurse specialist and included a one hour lecture/presentation 'A New Molecule in Diabetes – From Conception to Reality' delivered by a senior specialist, Novo Nordisk A/S.

COMPLAINT

Lilly alleged that this presentation involved the pre-licence discussion and promotion of liraglutide to health professionals. It appeared that Novo Nordisk had intentionally commercialised liraglutide by a keynote lecture to promote the product and create the misleading impression amongst the delegates that liraglutide was a licensed and relevant treatment option for the management of diabetes. This was evidenced by the context in which this particular lecture was presented ie preceded by an extensive discussion of subjects such as 'Diabetes – A Weighty Issue, New Treatments, Guidelines for Diabetes Care'.

In inter-company correspondence Novo Nordisk acknowledged that the keynote lecture by a Novo Nordisk employee focused on the development of liraglutide, hence the title 'From Conception to Reality'. Given the latter and the fact that this was clearly a Novo Nordisk sponsored promotional meeting, Lilly refuted Novo Nordisk's assertion that this meeting was 'a very useful educational meeting, rather than a promotional opportunity'.

Lilly alleged that this activity again constituted the pre-licence promotion of liraglutide, it invited misleading claims and comparisons with licensed medicines and represented the disguised promotion of liraglutide in breach of Clauses 3.1, 7.2, 7.3 and 12.1 and given the serious nature of the matter, breaches of Clauses 9.1 and 2.

RESPONSE

Novo Nordisk referred to inter-company dialogue in which it submitted that the symposium on diabetes care had been running for the past few years, and was widely regarded by attendees as a very useful educational meeting, rather than a promotional opportunity. The keynote lecture 'A New Molecule in Diabetes – From Conception to Reality' was delivered by a senior specialist at Novo Nordisk.

Novo Nordisk refuted Lilly's allegation that the aim of the keynote lecture was to promote liraglutide and create the misleading impression it was a licensed and relevant treatment option for the management of diabetes. The senior specialist clearly stated that liraglutide was not licensed. In addition, the topic of the presentation was the development of liraglutide, hence the title 'From Conception to Reality'; the senior specialist did not state or imply anything which could be perceived as promotional.

PANEL RULING

The Panel noted that Novo Nordisk was responsible for the meeting. The final presentation was the one at issue. The title 'A New Molecule in Diabetes – From Conception to Reality' implied that the new molecule (liraglutide) was available for use and this was not so. No details had been provided about the delegates. The Panel considered that the meeting would be considered as promotional given it was a Novo Nordisk meeting. The presentation by a Novo Nordisk employee needed to comply with the Code. The content referred to GLP-1 and its clinical potential as well as GLP-1 analogues. It included detailed information about liraglutide. The presentation compared liraglutide with exenatide,

vildagliptin, glimepiride, rosiglitazone and glargine. The last few slides compared liraglutide and exenatide in relation to HbA_{1c}, HOMA, body weight and frequency of nausea. Each parameter favoured liraglutide and the HbA_{1c} and HOMA data were statistically significant. The final slide showed advantages for exenatide compared with glargine in relation to a composite endpoint of $HbA_{1c} \leq 7.4\%$ and weight gain ≤ 1kg. There did not appear to be any mention of the licensed status of the product. The final slide concluded that GLP-1 based therapies were highly interesting for treatment for type 2 diabetes and that GLP analogues might be made once daily treatments.

The Panel considered that taking all the circumstances into account the keynote presentation constituted promotion of liraglutide at a time when it did not have a marketing authorization. Thus the Panel ruled a breach of Clause 3.1 as alleged. The title of the presentation was misleading. A breach of Clause 7.2 was ruled. The presentation included comparisons with licensed medicines and could be seen as taking unfair advantage of the reputation of licensed medicines thus a breach of Clause 7.3 was ruled. The Panel did not consider that the meeting constituted the disguised promotion of liraglutide. The presentation was clearly promotional and no breach of Clause 12.1 was ruled.

The Panel considered that high standards had not been maintained and ruled a breach of Clause 9.1. The Panel noted that promoting a medicine prior to the grant of the marketing authorization was an activity likely to be in breach of Clause 2. That clause was used as a sign of particular censure. The Panel ruled a breach of Clause 2.

4 An endocrine and diabetes society meeting, February 2009

Lilly was aware that Novo Nordisk in partnership with an endocrine and diabetes society was developing local research strategy involving collaboration between centres throughout the local area. To support this, a senior member of Novo Nordisk's sales department helped convene/facilitate the above company sponsored meeting which included discussion of liraglutide data in diabetes and obesity, the latest Levemir (insulin detemir) data, ongoing development/ research projects and opportunities for collaboration in areas of pharmacological research in the local area amongst other things. Novo Nordisk extended an open invitation for any health professionals interested in participating in collaborative research projects to attend.

COMPLAINT

Lilly alleged that this was clearly a promotional meeting sponsored by Novo Nordisk as evidenced by the tacit and direct involvement of sales and marketing staff; this was acknowledged by Novo Nordisk in inter-company correspondence. Lilly failed to understand why a member of the sales department would be involved in a meeting purporting to be focused on the information needs of 'potential and existing investigators' and where the objective was 'to update [delegates] on current and future research projects'.

Lilly alleged that the discussion of liraglutide data and other medicine development/research projects and data constituted pre-licence disguised promotion of liraglutide in breach of Clauses 3.1 and 12.1 and given the serious nature of the matter, breaches of Clauses 9.1 and 2.

RESPONSE

Novo Nordisk referred to inter-company dialogue in which it submitted that the meeting at issue was initiated by the endocrine and diabetes society which asked the senior member of its sales department for an update on ongoing and future research activities at Novo Nordisk. This request was forwarded to the clinical research department as it had strong links with the endocrine and diabetes society. Invited delegates were potential and existing investigators, and the aim of the meeting was to update them on current and future research projects within Novo Nordisk. With this in mind, it was entirely appropriate to talk about liraglutide data, latest Levemir data and other ongoing development/research projects, as it was made clear both by the purpose of the meeting and the individual presentations that this was an update on research and at no point were any promotional claims made, either directly or indirectly.

Novo Nordisk submitted that however, during the planning phase of this meeting, the clinical research department invited the senior member of the sales department to attend, purely in an observational role; he had no input into the content of the meeting, and did not take an active role at any point during the meeting. All parties had been reminded of the importance of the Code with relation to sales/marketing involvement and attendance at meetings where pre-licence or off-licence data was to be discussed.

Novo Nordisk provided a copy of a letter from the endocrine and diabetes society received after Novo Nordisk submitted its response on 22 June. Novo Nordisk submitted that this further confirmed that the meeting was not a Novo Nordisk initiative and Novo Nordisk did not have any intention to utilise it as a promotional platform.

PANEL RULING

The Panel noted that few details had been provided about this meeting. A presentation about 'On going development projects' had been given. The meeting appeared to have been held in response to an unsolicited request from the endocrine and diabetes society for an update on ongoing and future research projects. From the agenda all of the

speakers were from Novo Nordisk. The Panel was concerned that a senior member of the company's sales department had attended, albeit by invitation. The impression that that gave was important.

The Panel examined the slides used by Novo Nordisk for the presentation 'On going development projects'. The introduction referred to insulin research and development including future insulins and products Novo Nordisk was working on. It also referred to GLP-1 development. Information was presented about a study on islet transplantation which ran from April 2009.

The Panel was concerned that based on Novo Nordisk's activities already considered above, in particular points 1 and 2, it was possible that liraglutide had been promoted to the audience. The Panel considered that this meeting appeared to be different to the one at issue in point 3 above in that it was organised by Novo Nordisk in response to a request that the meeting be held. However the complainant had the burden of proving their complaint on the balance of probabilities. The Panel considered that given all the circumstances and the limited evidence before the Panel, the meeting could be regarded as the legitimate exchange of scientific information. Delegates were invited as potential or existing investigators, not as prescribers per se. No breach of Clauses 3.1 and 12.1 was ruled. The Panel also ruled no breach of Clauses 2 and 9.1.

5 Diabetes network meeting, March 2009

COMPLAINT

Lilly alleged that this promotional meeting sponsored by Novo Nordisk invited presentations and discussions about the management of patients with type 2 diabetes and presented information and various data about liraglutide, which, at the time, was unlicensed in the UK. A significant part of the meeting was devoted to a debate 'This house believes that GLP-1 agonists (such as exenatide and liraglutide) are the best second line therapy for type 2 diabetes'.

Further, Lilly alleged that the debate involved the presentation of liraglutide data to health professionals and engaged the audience in the pre-licence discussion of liraglutide and its place in the management of type 2 diabetes alongside licensed GLP-1-based therapies such as Byetta; this was misleading by implication as it implied that liraglutide was a licensed and relevant treatment option for the management of diabetes. The meeting was attended by Novo Nordisk sales representatives, which further exemplified the promotional nature of this meeting. Discussion of liraglutide, directly or indirectly, at this meeting was of commercial interest to Novo Nordisk.
Lilly alleged that reference to topics on new treatment options in diabetes, the incretin system, modulators or mimetics of GLP-1, GLP-1 receptor agonists and the dipeptidyl IV receptor antagonists, effectively solicited questions from delegates and discussion by the speakers on the availability of new treatments such as liraglutide thereby promoting the medicine to health professionals prior to the grant of the marketing authorization. Lilly questioned the validity of Novo Nordisk's assertion that only the regional medical advisor remained during the debate; this was contrary to the observations of Lilly staff who also attended this meeting.

Lilly alleged that this activity constituted the pre-licence promotion of liraglutide, it invited misleading claims and comparisons with licensed medicines and constituted the disguised promotion of liraglutide. As such it was in breach of Clause 3.1, 7.2, 7.3 and 12.1. Given the serious nature of the matter Lilly also alleged that this activity was in breach of Clauses 9.1 and 2.

RESPONSE

Novo Nordisk referred to inter-company dialogue in which it submitted that the meeting agenda and contents were organised by the diabetes network entirely independently of Novo Nordisk; the company's only involvement was to pay to the diabetes network to allow it to set up a promotional stand in the meeting room. Novo Nordisk understood that Lilly and Sanofi-Aventis similarly paid to have stands in the meeting room.

Novo Nordisk submitted that one hour of the meeting was dedicated to the debate 'This house believes that GLP-1 agonists (such as exenatide and liraglutide) are the best second line therapy for type 2 diabetes'. This debate was decided upon and organised entirely independently of Novo Nordisk, and it had no involvement in choice of speaker, slide selection or topics for discussion.

The meeting was attended by Novo Nordisk sales representatives and a regional medical advisor. Following lunch, and before the debate, the Novo Nordisk promotional stand was dismantled, and the sales representatives left the meeting room. The regional medical advisor had verbal permission from the meeting organiser to stay in the meeting room for the debate. It was made very clear by both presenters during the debate that liraglutide was unlicensed and that exenatide had been licensed. Due to Novo Nordisk's limited involvement in the organisation of the meeting, and the clear lack of involvement in the debate, the company firmly refuted the allegations that it had breached the Code.

Novo Nordisk submitted that as it had no involvement in choice of speakers, slide selection or topics for discussion it could not provide the slide sets used during the debate. The allegation that the meeting was attended by sales representatives was not correct. Although Novo Nordisk sales representatives were at the venue they left the auditorium before the debate started. The debate was only attended by the local regional medical

advisor from Novo Nordisk. Furthermore any promotional activity on the promotional stand which was located outside the auditorium ceased and the stand was dismantled before the debate started.

Novo Nordisk could not provide a list of attendees because the meeting was organized by local health professionals, not Novo Nordisk.

In response to a request for further information Novo Nordisk stated that the speakers were ultimately chosen by the main organiser of the meeting, who was also responsible for the meeting agenda. Novo Nordisk knew about the agenda and the topics at the beginning of February 2009 when local organisers forwarded it to the company.

PANEL RULING

The Panel was concerned about the arrangements for the meeting. Novo Nordisk knew about the agenda about a month before the meeting. The topic of the debate that agents such as exenatide and liraglutide were the best second line therapy for type 2 diabetes was of concern given that one product had a marketing authorization and the other did not but was about to be so authorized. The title of the debate implied that both products were licensed and this was not so.

The Panel noted that Novo Nordisk had denied the allegation that its sales representatives were present during the debate; Novo Nordisk submitted that only its local regional medical advisor was present. The Panel was concerned, given the title of the debate, that the regional medical advisor had attended even though Novo Nordisk submitted it had a clear lack of involvement in the debate. The Panel had similar concerns to those mentioned in point 4 above. Novo Nordisk stated that the speakers were ultimately chosen by the main organiser of the meeting. There was no evidence before the Panel about the extent to which, if at all, Novo Nordisk had been able to influence or comment upon speaker selection. However Novo Nordisk had no involvement in the slide selection or topics for discussion. The Panel did not consider that Novo Nordisk's payment for an exhibition stand at the meeting meant that Novo Nordisk had sponsored the meeting and was responsible for its content. The Panel noted its concerns about the title of the debate and Novo Nordisk's knowledge thereof. However, on the evidence before it, the Panel decided that Novo Nordisk was not responsible for content of this meeting and thus no breach of Clauses 3.1, 7.2, 7.3 and 12.1 was ruled. The Panel also ruled no breach of Clauses 2 and 9.1.

6 Annual Conference of a diabetes managed clinical network conference, April 2009

This meeting involved the discussion of various diabetes related topics by way of formal presentations and workshops and included a workshop focussing on the incretin mimetics.

COMPLAINT

Lilly alleged that although this meeting was facilitated by Novo Nordisk its sponsorship was not declared on the conference agenda. Novo Nordisk also had a promotional stand at the meeting and in particular, three of its sales representatives together with a sales manager attended the presentations and workshops which discussed incretin mimetics.

Lilly noted that in inter-company correspondence Novo Nordisk acknowledged that it 'helped fund the travel expenses of a visiting professor' and also did not ensure the necessary declaration of this sponsorship in relation to the meeting materials. This was attributed to error and the medical department not being told about the meeting.

Whilst the latter explanation offered no mitigation, Lilly questioned the validity of Novo Nordisk's assertion that the professor was invited by the diabetes managed clinical network independently of Novo Nordisk. Lilly had it on good authority that the professor's input was facilitated by Novo Nordisk and that this included payment of an honorarium. This could be disclosed should it be required.

Lilly alleged that the professor's presentation 'Emerging New therapies in Diabetes Care' involved an unbalanced discussion of Byetta and liraglutide and specifically invited a comparison of the two. In particular, reference was made to unpublished data derived from Novo Nordisk's Lead 6 study which involved a head-to-head comparison of Byetta and liraglutide. There was no clear indication of the licensed status of liraglutide and the impression created, by association to Byetta, was that liraglutide was available and a clinically relevant treatment option in the management of type 2 diabetes.

Lilly was also disappointed that both the speaker and Novo Nordisk disparaged Byetta throughout the presentation by referring to it as 'lizard spit'. Further, the discussion of Byetta was unbalanced and relatively abbreviated compared with the information provided on liraglutide. To compound matters the speaker also conveyed the message that Byetta was only a 50% homologous in comparison to human (physiological) GLP-1; although factually correct, the context in which this was discussed implied an inferior efficacy of Byetta in reducing blood glucose. The speaker also inferred that liraglutide was developed later than Byetta because Novo Nordisk had deliberately taken longer researching this medicine in a more scientific way and hence liraglutide 97% homologous with human GLP-1; the implication being that Lilly had not conducted proper scientific research leading to the development of inferior products such as Byetta.

This presentation and the attendant workshop represented the pre-licence and disguised promotion of liraglutide which was further illustrated by the discussion of data comparing

reduction of HbA_{1c} and weight loss data for Byetta and liraglutide. This was misleading as it implied, by association to Byetta, a licensed product, that liraglutide was also available and clinically relevant.

This activity constituted the pre-licence promotion of liraglutide, it invited misleading claims and comparisons with licensed medicines and constituted the disguised promotion of liraglutide. Lilly alleged breaches of Clauses 3.1, 7.2, 7.3, and 12.1 and, given the serious nature of the matter, a breach of Clauses 9.1 and 2.

Lilly alleged that it was evident that Case AUTH/2202/1/09 did not represent an isolated instance of the pre-licence promotion of liraglutide by Novo Nordisk but was part of a concerted commercially driven objective. The above examples clearly demonstrated that Novo Nordisk had consistently, intentionally and widely promoted the availability of liraglutide in the UK prior to the grant of a marketing authorization. It was also evident that both the medical department and sales department of Novo Nordisk had failed to enforce the necessary standards with regard to compliance with the Code and also, on the company's own admittance, its internal policies and procedures.

Given Novo Nordisk's failure to provide the requested undertakings and in the absence of any compelling or reasonable explanation to the contrary, Lilly alleged that all of the above Novo Nordisk sponsored activity constituted and evidenced the previous and ongoing pre-licence promotion of liraglutide to health professionals and therefore contravened the Code.

In response to a request for further information Lilly stated that the undisclosed information it had regarding the honorarium paid to the professor was obtained from the managed care network which verbally confirmed that it had been paid £800 by Novo Nordisk to cover the professor's honorarium as a speaker. The managed care network then paid the professor.

Further, Lilly alleged that a Novo Nordisk sales representative provided transport to the professor from the airport to the meeting and then onwards to another meeting; this clearly did not reconcile with Novo Nordisk's position that the diabetes managed clinical network selected and invited the speaker entirely independently of the company.

RESPONSE

Novo Nordisk referred to inter-company dialogue in which it submitted that the annual conference of the diabetes managed clinical network was arranged by that organisation itself. Novo Nordisk was asked to help fund the travel expenses of a visiting professor. The diabetes managed clinical network selected and invited the speaker entirely independently of Novo Nordisk. However, Novo Nordisk accepted that it should have declared this funding on the agenda/speaker slides. Novo Nordisk had a clear policy regarding the approval of meetings that it sponsored. Unfortunately, in this particular case it appeared that this had 'slipped through the net' and the medical department was not told of the meeting. Novo Nordisk was looking into the issues leading up to this error and would take steps to ensure that such did not occur again. The sales representatives involved had been reminded in the strongest terms of the importance of not being at or involved in meetings which discussed pre-licence or off-licence data.

In summary, Novo Nordisk prided itself on being a professional, responsible and ethical company, and on ensuring all activities complied with the Code. All staff received training and regular updates and adopted a rigorous approach to ensuring that activities fully complied with the Code.

Finally, Novo Nordisk stated that it had established a new legal and compliance department and one of its tasks was to review compliance procedures. As an initial step, an external consultant would audit the internal compliance procedures and advise as to how Novo Nordisk could confidently improve its processes. The consultant's detailed audit process was provided. This was confidential material. Novo Nordisk asked that the Authority did not reveal this document to Lilly. Novo Nordisk was confident that with the contribution of the new legal and compliance department and the help of its external consultant, it would further improve its internal process to ensure strict compliance with the Code and would help to avoid any future errors.

Furthermore Novo Nordisk submitted that its sales representatives did not have any promotional material concerning liraglutide, since such materials would clearly breach the Code as the product did not have a marketing authorization. A positive opinion from the Committee for Medicinal Products for Human Use for the approval of liraglutide in the treatment of type 2 diabetes was received on 23 April. The marketing authorization was expected to be granted on 29 June 2009.

Novo Nordisk could not provide a delegate list because this meeting was organized by local health professionals without involving Novo Nordisk in the process.

In response to a request for further information Novo Nordisk stated that it had tried, unsuccessfully, to contact the professor several times to clarify the source of the slides which showed unpublished Novo Nordisk data. Novo Nordisk still did not know where these materials came from but guessed that the most likely scenario was that the professor obtained the slides from a global advisory board organised by headquarter colleagues in Copenhagen.

PANEL RULING

The Panel noted that the professor's presentation included background information about GLP-1. A

slide of a Gila Monster lizard was included and another slide headed 'GLP-1 analogues-available/in development' stated that Byetta came from Gila saliva. The next product mentioned on this slide was liraglutide with details that it was once daily. There was no distinction as to which medicines had marketing authorizations and which did not. Similarly a slide headed 'Efficacy of incretin therapeutics' unfavourably compared HbA_{1c} and body weight loss for Byetta with that for liraglutide and included FPG decreases and HbA_{1c} reductions for Januvia (sitagliptin) and Galvus (vildagliptin). The only product that did not have a marketing authorization was liraglutide and again no mention of this difference was made in the slides. Two other slides showed statistically significant advantages for liraglutide over exenatide in reduction of HbA_{1c} and improvement in beta-cell function over 26 weeks. The final slides referred to the pipeline for type 2 diabetes therapy.

The Panel noted there was a discrepancy between the agenda which listed the presentation as 'Emerging New Therapies in Diabetes Care' and the slide presentation which was called 'Emerging drug therapies for diabetes making the alphabet work for T2DM'.

The Panel was extremely concerned about the arrangements for Novo Nordisk's involvement in this meeting. It was not clear from Novo Nordisk's submission whether it had paid travel expenses only or paid an honorarium as alleged by Lilly. The role, if any of a Novo Nordisk representative in providing/facilitating transport to and from the meeting was not clear. The agenda did not refer to Novo Nordisk's sponsorship of the professor. It was unacceptable for this not to be made clear on the documentation (Clause 19.3). In this regard the Panel considered that high standards had not been maintained and a breach of Clause 9.1 was ruled.

The Panel noted Novo Nordisk's submission that the meeting was arranged by the diabetes managed clinical network which had selected and invited the speaker entirely independently of Novo Nordisk. However Novo Nordisk had contributed to the costs of the professor. Companies could not fund or otherwise facilitate a speaker as a means of avoiding the requirements of the Code. Given the title of the professor's presentation 'Emerging New Therapies in Diabetes Care' and the role of Novo Nordisk it should have seen the materials prior to the presentation. The Panel was also concerned that Novo Nordisk was unsure as to where the professor had obtained Novo Nordisk unpublished material. Novo Nordisk should have checked the position with its head office.

Taking all the circumstances into account the Panel considered that, given Novo Nordisk's role, the sponsored presentation in effect promoted an unlicensed medicine. Thus a breach of Clause 3.1 of the Code was ruled. This was disguised promotion and breach of Clause 12.1 was also ruled. The material was misleading and included misleading comparisons. Breaches of Clauses 7.2 and 7.3 were ruled. High standards had not been maintained and a breach of Clause 9.1 was ruled.

The Panel noted that Novo Nordisk had facilitated the professor's attendance and that he had somehow been given access to the company's unpublished data on file. The company's association with the speaker should have been made clear to the delegates. Novo Nordisk's omission in this regard reduced confidence in and brought discredit upon the industry. A breach of Clause 2 was ruled.

* * * * *

The Panel was extremely concerned that Novo Nordisk had promoted a medicine prior to the grant of its marketing authorization on a number of occasions. There appeared, in general, to be a poor understanding of the requirements of the Code. Novo Nordisk had acknowledged that its procedures were lacking; communication at all levels within the company was inadequate. The Panel considered that the circumstances warranted reporting Novo Nordisk to the Code of Practice Appeal Board for it to consider the matter in accordance with Paragraph 8.2 of the Constitution and Procedure.

COMMENTS FROM NOVO NORDISK ON THE REPORT TO THE APPEAL BOARD

Novo Nordisk submitted that its compliance systems and procedures with regard to the Code were currently under extensive review and improvement.

Novo Nordisk stated that staff from its headquarters in Denmark were involved in the materials at issue in points 1 and 2 above (the educational website and the sponsored journal supplement respectively). Novo Nordisk UK understood that any material available to UK health professionals must comply with the Code. To this end it was developing detailed training and retraining programmes relating to relevant parts of the Code for its international colleagues to highlight the need to ensure that global material disseminated to a UK audience was reviewed and approved by Novo Nordisk UK to ensure compliance with the Code. Mandatory training was to be provided to corporate vice presidents in international marketing and medical affairs and international medical advisers whose responsibilities included the development of materials for publication by no later than 30 September.

Novo Nordisk UK's Legal and Compliance Manager was on Novo Nordisk's Global Legal and Compliance Board and the UK Marketing Director was a member of the Global Core Commercialisation Team. Both were completely committed to ensuring that the importance of compliance with the ABPI Code was continuously raised with international colleagues and the need to

ensure robust procedures, at a global level, was enforced to avoid further breaches by international colleagues.

Novo Nordisk submitted that the breaches of the Code in relation to the meetings Points 3 and 6 had further affirmed the need for it to reassess its in-house ABPI Code training programme. An external consultant had audited the company's compliance processes and procedures and highlighted the need to provide further Code training to staff. Novo Nordisk had therefore already put together in conjunction with the consultant an extensive mandatory training programme which it planned to roll out to all relevant staff at the UK office in September.

Novo Nordisk had also put in place a full training day for all diabetes field force (sales managers, diabetes care specialists, health development executives and regional medical advisors, etc) in October 2009. A draft agenda was provided. A representative of the Authority was invited to attend as an observer so that Novo Nordisk could demonstrate how seriously it was trying to improve its processes to ensure Code compliance. Novo Nordisk would welcome feedback in relation to its training programme. Novo Nordisk also noted that two of its senior physicians and a senior medical information officer would attend courses on the Code in September and October.

Novo Nordisk intended that by 8 October 2009, all relevant staff would have undertaken appropriate and relevant training in relation to the Code.

The Legal and Compliance Department had formed a Compliance Review Panel which would review and improve all policies and procedures which needed to comply with the Code. Any new or updated procedures would be rolled out, with appropriate training and validation via the Review Panel and/or Novo Nordisk's electronic training system. Ongoing refresher/updating Code training would take place at each of the field force sales conferences (three times annually) and quarterly for Novo Nordisk's UK marketing and medical staff.

Novo Nordisk hoped that the rigorous review of its global and UK procedures, together with its training programme demonstrated its commitment to address the failings with regard to the Code which had been highlighted by the Panel, and would go some way to ensure, as far as possible, that future breaches of the Code would be avoided.

APPEAL BOARD CONSIDERATION

The Appeal Board was extremely concerned about this case; the promotion of a medicine prior to the grant of its marketing authorization was a serious matter and displayed a poor understanding of the requirements of the Code. As well as being prohibited by the ABPI Code, it was also prohibited by the EFPIA Code on the Promotion of Prescription Only Medicines to, and Interactions with, Health Professionals. Headquarters staff in Denmark should know about the EFPIA Code. According to Novo Nordisk the website had been subjected to regulatory and legal review. The Appeal Board was not convinced that Novo Nordisk fully understood the seriousness of the matter and was especially concerned to note that the company had recently been found in breach of the Code for promoting liraglutide prior to the grant of its marketing authorization (Case AUTH/2202/1/09).

The Appeal Board noted that as a result of the rulings in this case Novo Nordisk had instigated a major review of its compliance systems, procedures and training. Code training of headquarters' staff was soon to be conducted by teleconference although the Appeal Board queried whether this was an effective training medium, given the seriousness of the case. The Appeal Board was very concerned about the apparent lack of influence that Novo Nordisk in the UK had over its headquarters in Denmark regarding compliance of material which came within the scope of the UK Code.

The Appeal Board decided in accordance with Paragraph 11.3 of the Constitution and Procedure to require an audit of Novo Nordisk's procedures in relation to the Code to be carried out by the Authority. The audit should be conducted as soon as possible. The Appeal Board suggested that relevant staff from Denmark should be interviewed as part of that audit. On receipt of the audit report the Appeal Board would consider whether further sanctions, including a report to the ABPI Board of Management, were necessary. In addition the Appeal Board decided that Novo Nordisk should be publicly reprimanded.

APPEAL BOARD FURTHER CONSIDERATION

The Appeal Board noted that it had previously decided that Novo Nordisk should be publicly reprimanded.

The Appeal Board was very concerned that as demonstrated in the audit reports of 2004/05 and the October 2009 audit report, Novo Nordisk clearly lacked processes to ensure compliance with the Code. This must be a priority for all including senior staff who must take more personal responsibility. The company must be able to show that this time it could change and develop attitudes and procedures which gave strong support to compliance.

The Appeal Board noted that Novo Nordisk was due to roll out a number of new standard operating procedures (SOPs) with training on them to commence early in 2010. This timeframe had been extended since the audit. The Appeal Board decided that in accordance with Paragraph 11.3 of the Constitution and Procedure to require a further audit of Novo Nordisk's procedures in relation to the Code to be carried out by the Authority. The audit should be conducted in March 2010 when the Appeal Board expected Novo Nordisk's awareness of the Code and processes including the SOPs to be

much improved and more embedded within the company. The re-audit in this case would take place at the same time as the audit required in Case AUTH/2269/9/09. On receipt of the audit report the Appeal Board would decide if further sanctions were necessary.

Upon receipt of the March 2010 audit report the Appeal Board considered that Novo Nordisk's progress was not sufficiently rapid. It still had serious concerns about the company's approach and attitude to the Code. There were still significant problems with certification. Not all the standard operating procedures (SOPs) had been completed and trained out. This was now due to happen at the May sales conference (other than the SOP for medical and educational goods and services).

Overall, the Appeal Board considered that Novo Nordisk still did not appear to appreciate the seriousness of the situation. The Appeal Board considered requiring Novo Nordisk to submit material for pre-vetting as set out in Paragraph 11.3 of the Constitution and Procedure and/or report the company to the ABPI Board of Management. The Appeal Board decided to require another audit in June/July. On receipt of that audit report the Appeal Board would decide whether further sanctions, such as pre-vetting and/or a report to the ABPI Board, were necessary.

Upon receipt of the July 2010 audit report the Appeal Board was concerned that it had taken some time but considered that significant progress had now been made. This must be maintained. The Appeal Board considered carefully all the options available noting that it had already decided that both cases (Cases AUTH/2234/5/09 and AUTH/2269/9/09) should be the subject of a public reprimand. It decided that no further action was necessary.

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