SPECIALIST DIABETES REGISTRAR v NOVO NORDISK

Promotion of Victoza

A specialist registrar in diabetes complained that, having recently undertaken some continuing medical educational (CME) sponsored by Novo Nordisk, he had received a follow-up email about Victoza (liraglutide) from a third party provider in the US. The email thanked the complainant for viewing the CME module 'Role of GLP-1 [Glucagon-like peptide-1] Agonists in Type 2 Diabetes Therapy' supported by an independent educational grant from Novo Nordisk, Inc. A number of key discussion points were listed in the email.

Whilst the complainant welcomed the educational opportunity he was concerned that this had been hijacked to promote liraglutide. For example, the email referred to the LEAD-6 study but there was an ambiguity and lack of clarity about the precise doses of the medicines used in that study which was misleading as was the suggestion that liraglutide was specifically recommended in the US and European guidelines cited. There was also ambiguity in the discussion of the comparative efficacy and safety of liraglutide vs exenatide which was misleading. The complainant was more seriously concerned about the misleading and incorrect safety information about the use of liraglutide in patients with renal disease.

In the CME module, a section entitled 'Differentiating Incretin Therapies: Focus on Liraglutide' stated that 'As exenatide is extensively cleared by the kidneys, it is not recommended in patients with a creatinine clearance below 30ml/minute or in those with [end-stage renal disease]. In contrast, the pharmacokinetics of liraglutide are unchanged in patients with different stages of renal impairment and treatment with liraglutide was not associated with an increased risk of adverse events'.

This was at odds with the liraglutide prescribing information which was not provided. The latter stated: 'Renal impairment: No dose adjustment is required for patients with mild renal impairment (creatinine clearance 60-90ml/min). There is very limited therapeutic experience in patients with moderate renal impairment (creatinine clearance of 30-59ml/min) and no therapeutic experience in patients with severe renal impairment (creatinine clearance below 30ml/min). Victoza can currently not be recommended for use in patients with moderate and severe renal impairment including patients with end stage renal disease (see section 5.2)'.

The complainant stated that this misinformation endangered patients and was unacceptable particularly when disseminated in the guise of education. The complainant was certain that the notable and authoritative signatures to the email in question would not have endorsed the information.

In response to a request for further information, the complainant stated that he had completed a form and provided his email and acknowledged his interest in being contacted by the US provider in relation to this particular module, amongst others; this form was available at a Novo Nordisk stand at a meeting in December 2009. Subsequently, he was invited to complete an online registration following an email from the US provider and he also agreed to receive updates for other diabetes related CME modules. He had also been given, by the company's sales representatives, a similar form, more recently when he attended two meetings jointly organised by Novo Nordisk and a UK third party education provider.

The detailed response from Novo Nordisk is given below.

The Panel noted that the complainant had stated that he had completed a form indicating his interest in the module at issue; he alleged that the form was available on the Novo Nordisk UK stand at a meeting in December 2009. He had subsequently been offered another form at two meetings jointly organised by Novo Nordisk and a UK third party education provider. Novo Nordisk denied that there were any forms or materials on its stands at the two meetings in December 2009 which invited attendees to register for the module in question or any other educational programme provided by the US provider. Novo Nordisk also submitted it was highly unlikely that the UK provider would offer services from the US provider. Novo Nordisk stated that it had not told any UK health professionals about the US programme.

The Panel noted the difference in the parties' accounts regarding the role of Novo Nordisk in the UK and considered that it was difficult to take this case further. The complainant was not prepared to disclose his identity; the identity of the Novo Nordisk representatives alleged to have given him the form was unknown. The Panel noted that the complainant had agreed to receive updates from the US third party provider for other diabetes related modules.

The Panel noted that the programme was sponsored by Novo Nordisk Inc in the US; Novo Nordisk UK submitted that it had not directed any UK health professional to the site. The Panel noted that nonetheless Novo Nordisk UK was responsible under the Code for the acts or omissions of its overseas affiliates that came within the scope of the Code. The email received by the complainant referred to the FDA, ie US, approval of Victoza, as of January 2010. Victoza had, however, been

available in the UK since 30 June 2009. It thus appeared that the email was directed to a US audience. There was no evidence that Novo Nordisk in the US had encouraged UK health professionals to register for the module in question. The activities of Novo Nordisk Inc in the US with non UK health professionals was not covered by the Code. Nevertheless the Panel was concerned about the allegations which related to the appropriate use of Victoza in renal impairment.

Noting that that a complainant had the burden of proving a complaint on the balance of probabilities, the Panel considered that, on the information provided, there had been no breach of the Code.

A specialist registrar in diabetes complained about the promotion of Victoza (liraglutide) by Novo Nordisk Limited.

COMPLAINT

The complainant had recently undertaken some continuing medical education (CME) training sponsored by Novo Nordisk and had received the following email sent by a third party provider in the US:

'Thank you for recently viewing the following activity on [US third party provider]: Role of GLP-1 [Glucagon-like peptide-1] Agonists in Type 2 Diabetes Therapy. Supported by an independent educational grant from Novo Nordisk, Inc.

To reinforce the educational impact of this activity, the key discussion points are listed below:

> Despite considerable advances in diabetes therapy over the last 10 years and the development of new treatment guidelines to help clinicians make the right therapeutic choices for their patients, many people with type 2 diabetes do not reach the glycemic target set by the ADA/EASD [American Diabetes Association/European Association for the Study of Diabetes].
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> Once-daily liraglutide FDA [Food and Drug Administration] approved as of January 2010) and twice-daily exenatide belong to the newest class of diabetes drugs, known as GLP-1 receptor agonists.
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> They address many of the unmet needs of diabetes patients, including weight loss, low risk of hypoglycemia, and ease of use. Consequently, they are likely to become prominent therapeutic tools in the treatment of type 2 diabetes. Current ADA/EASD guidelines recommend GLP-1 receptor agonists as second-line therapeutics, after metformin and sulphonylurea treatment have failed to maintain glycemic targets.
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> The [Liraglutide Effect and Action in Diabetes] LEAD-6 study is the first head-to-head comparison of liraglutide and exenatide. It was designed to directly compare the safety and efficacy of liraglutide and exenatide in a 26-week, randomized, open-label study. LEAD-6 data showed that liraglutide was significantly more effective at reducing glycated haemoglobin (HbA1c) levels than exenatide, and that more patients achieved HbA1c targets with liraglutide. Fasting plasma glucose reduction was also superior with liraglutide; however, exenatide was more effective at controlling postprandial blood glucose. Weight loss was comparable between treatment groups, whereas beta-cell function improvement was more significant in the liraglutide group.
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> In terms of safety, hypoglycaemia was significantly less frequent with liraglutide, and other adverse events were similar between treatment groups. Nausea was the main adverse event for both treatment groups but was less persistent with liraglutide than with exenatide. The results of the LEAD-6 study suggest that once-daily liraglutide may be more effective and better tolerated than twice-daily exenatide when added to metformin and/or sulphonylureas. However, exenatide may be more suitable for patients experiencing particularly high postprandial glucose levels. These findings were consistent with indirect comparisons of early-phase studies of the two therapies.
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> GLP-1 receptor agonists are likely to replace sulphonylureas in early treatment in many patients with type 2 diabetes in the future.
>
> These therapies may also have a role in combination with basal insulin once more data emerge. Additional GLP-1 receptor agonists are currently in development, including once-weekly formulations.'

Whilst the complainant welcomed the educational opportunity he was concerned that this had been hijacked to promote liraglutide. For example, the ambiguity and lack of clarity about the precise doses of the medicines used in the LEAD-6 study was very misleading as was the suggestion that this medicine was specifically recommended in the guidelines mentioned; it was not even mentioned in the National Institute for Health and Clinical Excellence (NICE) guidelines whereas exenatide was. The discussion of the comparative efficacy and safety of the two GLP-1 agonists was ambiguous and misleading. The complainant was more seriously concerned about the misleading and incorrect safety information about the use of this medicine in patients with renal disease.

In the CME module, a section entitled 'Differentiating Incretin Therapies: Focus on Liraglutide', stated that 'As exenatide is extensively cleared by the kidneys, it is not recommended in patients with a creatinine clearance below 30ml/minute or in those with ESRD [end-stage renal disease]. In contrast, the pharmacokinetics of liraglutide are unchanged in patients with different stages of renal impairment and treatment with liraglutide was not associated with an increased risk

of adverse events'.

This was at odds with the liraglutide prescribing information which was not provided. The latter stated that 'Renal impairment: No dose adjustment is required for patients with mild renal impairment (creatinine clearance 60-90ml/min). There is very limited therapeutic experience in patients with moderate renal impairment (creatinine clearance of 30-59ml/min) and no therapeutic experience in patients with severe renal impairment (creatinine clearance below 30ml/min). Victoza can currently not be recommended for use in patients with moderate and severe renal impairment including patients with end stage renal disease (see section 5.2)'.

The complainant stated that this misinformation endangered patients and was unacceptable particularly when disseminated in the guise of education. The complainant was certain that the notable and authoritative signatures to the email above would not have endorsed this questionable information.

When writing to Novo Nordisk, the Authority asked it to comment in relation to Clauses 2, 4.1, 7.2, 7.3, 7.4, 7.9, 9.1, 9.9 and 12.1 of the Code.

RESPONSE

Novo Nordisk noted that the complaint concerned a US third party online educational programme 'Role of GLP-1 Agonists in Type 2 Diabetes Therapy'.

Novo Nordisk did not know about the programme until it received the complaint, and as such Novo Nordisk Limited (UK) did not influence its content or development. Given this was not a UK-initiated site, it had not been certified for use within the UK and Novo Nordisk Limited had not told any UK health professionals about the programme.

The programme referred to the involvement of Novo Nordisk Inc, which was part of the Novo Nordisk Group based in the US. Novo Nordisk understood that Novo Nordisk Inc had not directed any UK health professionals to this site. Novo Nordisk had no way of knowing whether the complainant or any other UK health professionals found the programme as a result of a self-initiated internet search or had received an email regarding its availability. Novo Nordisk understood that the US third party provider might communicate with its registered users – a copy of its registration form which all health professionals were required to complete before gaining access to the website was provided. This included explicit consent for materials relevant to the health professional's area of expertise to be emailed to them.

Given that Novo Nordisk had not influenced the sponsorship, content, development or promotion of the programme, and it understood that Novo Nordisk Inc had not promoted this site to UK health professionals, Novo Nordisk denied breaches of Clauses 2, 4.1, 7.2, 7.3, 7.4, 9.1 and 12.1.

Novo Nordisk further noted that the authors of the email in question were not employees of Novo Nordisk Limited, nor of Novo Nordisk Inc.

FURTHER COMMENTS FROM THE COMPLAINANT

The Panel asked the complainant how he knew about the modules and whether he had signed any agreement with the US third party to access its educational modules that included giving permission to receive follow-up emails.

The complainant stated that he had completed a form and provided his email and acknowledged his interest in being contacted in relation to this particular module, amongst others; this form was available at the Novo Nordisk stand at the December 2009 meeting of the UK Primary Care Diabetes Society (PCDS). Subsequently, he was invited to complete an online registration following an email from the US third party during which he also agreed to receive updates for other diabetes related CME modules. He had also been given, by the company's sales representatives, a similar form, more recently when he attended two meetings jointly organised by Novo Nordisk and a UK third party education provider which he did not require as he was already registered with the US provider.

Novo Nordisk was invited to comment on this information.

FURTHER COMMENTS FROM NOVO NORDISK

In relation to the December UK PCDS meeting, Novo Nordisk stated that it sponsored a satellite symposium prior to the 2009 Scottish PCDS Conference 'Type 2 Diabetes' held in Glasgow on 7 December 2009 and secondly the 'Diabetes Inpatient Conference' in London on 14 December 2009. Copies of the registration forms, together with the agendas for these meetings, were provided. Novo Nordisk confirmed that no forms or information on the stands of either of these meetings invited attendees to register for the US educational modules at issue.

Novo Nordisk stated that it worked with the UK third party education provider from time to time. A copy of the flyer which highlighted the 2010 Insulin Management Workshops, sponsored by Novo Nordisk, was provided. This was the only material which Novo Nordisk's sales representatives had been given in relation to these joint meetings.

Novo Nordisk noted that the UK third party education provider it worked with and the US one named by the complainant were direct competitors; it was highly unlikely that the UK provider would have any information concerning US services at its meetings.

At each of the meetings referred to by the complainant, a standard set of materials was on the Novo Nordisk stands. Details were provided.

Novo Nordisk was concerned that the complainant had made unsubstantiated allegations, given that he had not provided the forms at issue and could not clarify as to where he had obtained them. In order for Novo Nordisk to instigate a proper investigation it needed details from the complainant as to which meetings he was referring to, so that it could check its systems in relation to the documented activities of its sales representative in the relevant geographical area etc on the relevant dates.

PANEL RULING

The Panel noted that the complainant had stated that he had completed a form indicating his interest in the US module at issue; he alleged that the form was available on the Novo Nordisk UK stand at a meeting in December 2009. He had subsequently been offered another form at two meetings jointly organised by Novo Nordisk and a UK third party education provider. Novo Nordisk denied that there were any forms or materials on its stands at the two meetings in December 2009 inviting attendees to register for the US module in question or any other educational programme provided by the US provider. Novo Nordisk also submitted it was highly unlikely that the UK third party education provider it worked with would offer the competitor's services. Novo Nordisk stated that it had not told any UK health professionals about the US programme.

The Panel noted the difference in the parties' accounts regarding the role of Novo Nordisk in the UK and considered that it was difficult to take this case further. The complainant was not prepared to disclose his identity to Novo Nordisk and the identity of the Novo Nordisk representatives alleged to have given him the form was unknown. The Panel noted that the complainant had agreed to receive updates from the US provider for other diabetes related modules.

The Panel noted that the programme was sponsored by Novo Nordisk Inc in the US; Novo Nordisk UK submitted that it had not directed any UK health professional to the site. The Panel noted that nonetheless Novo Nordisk UK was responsible under the Code for the acts or omissions of its overseas affiliates that came within the scope of the Code. The US email received by the complainant referred to the FDA, ie US, approval of Victoza, as of January 2010. Victoza had, however, been available in the UK since 30 June 2009. It thus appeared that the email was directed to a US audience. There was no evidence that Novo Nordisk in the US had encouraged UK health professionals to register for the module in question. The activities of Novo Nordisk Inc in the US with non UK health professionals was not covered by the Code. Nevertheless the Panel was concerned about the allegations which related to the appropriate use of Victoza in renal impairment.

Noting that that a complainant had the burden of proving a complaint on the balance of probabilities, the Panel considered that, on the information provided, there had been no breach of the Code. Thus the Panel ruled no breach of Clauses 2, 4.1, 7.2, 7.3, 7.4, 7.9, 9.1, 9.9, and 12.1.

Complaint received **18 May 2010**

Case completed **16 August 2010**