CASE AUTH/3033/4/18 ***NO BREACH OF THE CODE***

BOEHRINGER INGELHEIM and LILLY v NOVO NORDISK

Promotion of Victoza

Boehringer Ingelheim Limited and Eli Lilly and Company Limited (the Alliance) complained about the promotion of Victoza (liraglutide) by Novo Nordisk. The material at issue was an exhibition panel (ref UK/VT/0318/0108) used by Novo Nordisk at the Diabetes UK Professional Congress, March 2018. Victoza was a glucagon-like peptide-1 receptor agonist (GLP-1 RA) indicated for the treatment of adults with insufficiently controlled type 2 diabetes as an adjunct to diet and exercise.

The Victoza summary of product characteristics (SPC) stated it could be used as monotherapy when metformin was considered inappropriate due to intolerance or contraindications and could be used in addition to other medicinal products for the treatment of diabetes. Section 4.1 of the SPC also stated that study results with respect to combinations, effects on glycaemic control and cardiovascular (CV) events and the populations studied could be found in Sections 4.4, 4.5 and 5.1 of the SPC.

Two thirds of the exhibition panel featured the photograph of a woman walking in the shade towards the viewer and about to turn left around the corner of a large building and into what appeared to be a sunnier aspect. Wrapping around the corner of the building was the text 'In adults with insufficiently controlled type 2 diabetes change the course of treatment by reducing CV [cardiovascular] risk'. This was followed by red text which was mostly about the same height as the woman and which read 'HbA1CV' such that 'CV' was in the foreground of the picture. The headline across the top of the picture read 'Victoza: the only GLP-1 RA superior in preventing CV events vs placebo'. To the right side of the picture, and in the remaining third of the panel were the following two paragraphs in bold font:

> **'Indication : Victoza is indicated for the treatment of adults with insufficiently controlled type 2 diabetes as an adjunct to diet and exercise.**
>
> **Section 5.1: Both improvement of glycaemic control and reduction of CV morbidity and mortality are an integral part of the treatment of type 2 diabetes.'**

The detailed response from Novo Nordisk is given below.

The Alliance alleged that the overall prominence of the two main claims on the stand 'Change the course of treatment by reducing CV risk' and 'Victoza: the only GLP-1 RA superior in preventing CV events vs placebo' combined with the imagery, would lead observers to conclude that the promotional message was weighted heavily towards the reduction of CV risk. Victoza was not indicated for the reduction of CV risk but for the treatment of adults with insufficiently controlled type 2 diabetes as an adjunct to diet and exercise. The CV benefits of Victoza were referred to only in Section 5 of the SPC and so

should be promoted as added benefits of Victoza rather than as the main indication. The Alliance alleged that the overall balance of the stand promoted Victoza inconsistently with the SPC.

The Panel noted that Victoza had been available as a treatment for diabetes for a number of years. According to Novo Nordisk the SPC had been updated in July 2017 following Marso *et al*, a cardiovascular outcomes trial for Victoza in type 2 diabetes patients with high CV risk (LEADER). Section 5.1 of the SPC which included a section headed 'cardiovascular evaluation' with data from LEADER did not mention that the patients had high CV risk. An earlier part of Section 5.1, headed clinical efficacy and safety, referred to LEADER as a large cardiovascular outcomes trial in 9340 type 2 diabetes patients at high cardiovascular risk. The EMA assessment report referred to the need to include the patient population (Type 2 diabetes) in the indication. The improvement of glycaemic control and the reduction of cardiovascular morbidity and mortality were an integral part of treatment of type 2 diabetes, best expressed in a single indication. A separate cardiovascular prevention indication was not therefore appropriate.

It appeared to the Panel that the exhibition stand was a three dimensional advertisement with the woman and large building part being separated from the rest of the advertisement which framed the picture of the woman and the building. The top of the frame and the right hand side promoted Victoza. The Panel agreed that the message from the exhibition stand was in relation to CV risk. This was set within the context of the treatment of type 2 diabetes. Both parts of the exhibition stand referred to type 2 diabetes and the frame part of the exhibition stand included the indication and details from Section 5.1 of the SPC. The Panel noted that visitors to the stand would be attending the Diabetes UK Professional Congress.

The Panel did not consider that the exhibition stand was unambiguously clear as submitted by Novo Nordisk. However, the Panel considered that on balance, taken as a whole the exhibition stand was not inconsistent with the SPC as alleged and no breach was ruled. The stand overall was not misleading as alleged thus the Panel ruled no breach of the Code.

The Alliance alleged that the claim 'Change the course of treatment by reducing CV risk' promoted Victoza's additional CV benefits as the primary reason to prescribe. This call to action was misleading and inconsistent with the SPC as it put undue emphasis on CV benefits observed in a clinical trial.

The Alliance noted that the main imagery of the exhibition panel depicted a pavement, adjacent to which was a wall with the word 'HbA1CV'. A woman (presumably a type 2 diabetic) was walking down a shaded pavement, marked by HbA1c, about to turn a corner into the light part of the pavement marked CV. This suggested that Victoza's added benefits with respect to CV risk were at least equally important as the licensed indication, which was glycaemic control of HbA1c. Together with the above claim, the Alliance alleged that this was misleading and inconsistent with the SPC.

The Panel considered that the important factor was that the patient had type 2 diabetes. The outcome of the CV study would be of interest to those that treated type 2 diabetes. There was a change in the Victoza SPC and the company was fully entitled to draw attention to that change. The benefits shown in the LEADER trial were in relation to high

cardiovascular risk patients. The Victoza SPC also referred to more general information which showed no increase in CV risk for liraglutide versus all comparators.

The Panel considered that the claim 'Change the course of treatment by reducing CV risk' in conjunction with 'HbA1CV' emphasised the CV risk reduction with Victoza. However the context and audience were important. The frame part of the stand referred to a qualifcation, 'In adults with type 2 diabetes and high CV risk...'. Given its ruling in point 1 above and taking all the circumstances into account the Panel did not consider that Novo Nordisk was promoting the additional CV benefits as the primary reason to prescribe Victoza as alleged. In the Panel's view the mention of the CV benefits was not misleading or inconsistent with the SPC as alleged. The Panel ruled no breach of the Code. The stand was not misleading in this regard and no breach was ruled.

The Alliance alleged that given the position taken by Novo Nordisk during inter-company dialogue, Novo Nordisk had failed to maintain high standards and reduced confidence in the industry, in breach of the Code. Novo Nordisk's promotional stand for Victoza at the Diabetes UK Professional Conference on 13 March 2018 demonstrated that it continued to promote Victoza in the manner complained about in inter-company dialogue.

The Panel noted the important role of inter-company dialogue. Novo Nordisk had withdrawn a leavepiece without prejudice. There were similarities between the leavepiece at issue in the inter-company dialogue and the exhibition stand, the subject of the complaint to the PMCPA. However, Novo Nordisk had not agreed with The Alliance's view that the leavepiece was in breach of the Code. It was disappointing that Novo Nordisk had not given The Alliance more details. Novo Nordisk's letter of 4 January stated that the company now considered the inter-company matter resolved. In the light of the content of the exhibition stand it appeared that The Alliance considered that the inter-company matter was not resolved. The Panel appreciated the frustration for companies when issues raised and considered resolved at inter-company level appeared again in a different format. The main difference with the photograph of the women turning the corner related to the claim 'In adults with type 2 diabetes' used in the leavepiece had been amended to 'In adults with insufficiently controlled type 2 diabetes; in the exhibition stand. The Panel considered that there were differences between the leavepiece and the exhibition stand. It did not accept that Novo Nordisk failed to maintain high standards as alleged and ruled no breach of the Code.

Boehringer Ingelheim Limited and Eli Lilly and Company Limited (the Alliance) complained about the promotion of Victoza (liraglutide) by Novo Nordisk. The material at issue was an exhibition panel (ref UK/VT/0318/0108) used by Novo Nordisk at the Diabetes UK Professional Congress, 14-16 March 2018. Victoza was a glucagon-like peptide-1 receptor agonist (GLP-1 RA) indicated for the treatment of adults with insufficiently controlled type 2 diabetes as an adjunct to diet and exercise.

The Victoza summary of product characteristics (SPC) stated it could be used as monotherapy when metformin was considered inappropriate due to intolerance or contraindications and could be used in addition to other medicinal products for the treatment of diabetes. Section 4.1 of the SPC also stated that study results with respect to combinations, effects on glycaemic control and cardiovascular (CV) events and the populations studied could be found in Sections 4.4, 4.5 and 5.1 of the SPC.

Two thirds of the exhibition panel featured the photograph of a woman walking in the shade towards the viewer and about to turn left around the corner of a large building and into what appeared to be a sunnier aspect. Wrapping around the corner of the building was the text 'In adults with insufficiently controlled type 2 diabetes change the course of treatment by reducing CV [cardiovascular] risk'. This was followed by red text which was mostly about the same height as the woman and which read 'HbA1CV' such that 'CV' was in the foreground of the picture. The headline across the top of the picture read 'Victoza: the only GLP-1 RA superior in preventing CV events vs placebo'. To the right side of the picture, and in the remaining third of the panel were the following two paragraphs in bold font:

> 'Indication : Victoza is indicated for the treatment of adults with insufficiently controlled type 2 diabetes as an adjunct to diet and exercise.
>
> Section 5.1: Both improvement of glycaemic control and reduction of CV morbidity and mortality are an integral part of the treatment of type 2 diabetes.'

Boehringer Ingelheim's Product Jardiance (empagliflozin) a selective inhibitor of sodium-glucose co-transporter 2 (SGLT2) was promoted by The Alliance. Jardiance was indicated for the treatment of adults with insufficiently controlled type 2 diabetes melitis as an adjuct to diet and exercise. Section 4.1 of its SPC referred to, *inter alia*, cardiovascular events, and cross referred to other sections of the SPC. Section 5.1 of the Jardiance SPC referred to cardiovascular outcomes.

1 Overall balance of the stand

COMPLAINT

The Alliance noted that the two main claims on the stand read 'Change the course of treatment by reducing CV risk' and 'Victoza: the only GLP-1 RA superior in preventing CV events vs placebo'. The Alliance alleged that overall prominence of these claims, combined with the imagery, would lead observers to conclude that the promotional message of the stand was weighted heavily towards the reduction of CV risk. The Alliance noted that Victoza was not indicated for the reduction of CV risk but for the treatment of adults with insufficiently controlled type 2 diabetes as an adjunct to diet and exercise. The CV benefits of Victoza were referred to only in Section 5 of the summary of product characteristics (SPC) and so they should be promoted as added benefits of Victoza rather than as the main indication. The Alliance alleged that the overall balance of the stand promoted Victoza inconsistently with the SPC and in breach of Clauses 3.2, 7.2 and 7.8.

RESPONSE

Novo Nordisk noted that Victoza was not indicated for the reduction of CV risk in isolation and it had not promoted it as such. The claims at issue highlighted the results of the LEADER (The liraglutide effect and action in diabetes evaluation of cardiovascular outcomes results) study, a cardiovascular outcomes trial for Victoza (Marso *et al* 2016). The claims were made in the context of the treatment of type 2 diabetes and the indication for Victoza.

The indication for Victoza was clearly stated in bold type on the right hand side of the exhibition panel. In addition, the statement 'in adults with type 2 diabetes and high CV risk when added to standard of care as demonstrated in the LEADER study' appeared below the headline claim

'Victoza: the only GLP-1 RA superior in preventing CV events vs placebo'. Any mention of 'reducing CV risk' did not suggest CV benefit as a main indication for Victoza, but rather as an inclusive part of the product attribute within the licensed indication for the treatment of adults with type 2 diabetes. This was unambiguously clear.

Novo Nordisk submitted that the Committee for Medicinal Products for Human Use (CHMP) recommended strengthening of the wording of the indication by deleting 'improvement of glycaemic control' from Section 4.1 of the Victoza SPC, as this restriction no longer adequately reflected the demonstrated effects of Victoza. This change in wording was recommended following the incorporation of the results from Marso *et al* in the Victoza European Public Assessment Report EPAR (copy provided).

The European Medicines Agency (EMA) considered that both improvement of glycaemic control and reduction of CV morbidity and mortality were integral to the treatment of type 2 diabetes, which could best be expressed in a single indication for Victoza. The changed wording in Section 4.1 of the Victoza SPC as well as the additional wording in Section 5.1, which further explained the role of glycaemia and CV risk in type 2 diabetes therapy, reflected the regulatory agency's view that a more holistic treatment approach was needed when treating type 2 diabetics.

Novo Nordisk submitted that based on the above, the claims used on the exhibition panel were not misleading or inconsistent with the Victoza SPC and hence there was no breach of Clauses 3.2, 7.2 and 7.8 of the Code.

PANEL RULING

The Panel noted that Clause 3.2 required that the promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its SPC.

The Panel noted that Victoza had been available as a treatment for diabetes for a number of years. According to Novo Nordisk the SPC had been updated in July 2017 following Marso *et al* which was a cardiovascular outcomes trial for Victoza in type 2 diabetes patients with high CV risk. Section 5.1 of the SPC which included a section headed 'cardiovascular evaluation' with data from LEADER did not mention that the patients had high CV risk. An earlier part of Section 5.1, headed clinical efficacy and safety, referred to LEADER as a large cardiovascular outcomes trial in 9340 type 2 diabetes patients at high cardiovascular risk. The EMA assessment report referred to the need to include the patient population (Type 2 diabetes) in the indication. The improvement of glycaemic control and the reduction of cardiovascular morbidity and mortality were an integral part of treatment of type 2 diabetes, best expressed in a single indication. A separate cardiovascular prevention indication was not therefore appropriate.

The Panel considered the description of the exhibition stand and the photographs provided. It appeared to be a three dimensional advertisement with the woman and large building part being separated from the rest of the advertisement which framed the picture of the woman and the building. The frame part included on the left side an advertisement for Xultophy, (insulin degludec and liraglutide) the top of the frame and the right hand side promoted Victoza. The Panel agreed that the message from the exhibition stand was in relation to CV risk. This was set within the context of the treatment of type 2 diabetes. Both parts of the exhibition stand referred to type 2 diabetes and the frame part of the exhibition stand included the indication and

details from Section 5.1 of the SPC. The Panel noted that visitors to the stand would be attending the Diabetes UK Professional Congress.

The Panel did not consider that the exhibition stand was unambiguously clear as submitted by Novo Nordisk. However, the Panel considered that on balance, taken as a whole the exhibition stand was not inconsistent with the SPC as alleged and no breach of Clause 3.2 was ruled. The stand overall was not misleading as alleged thus the Panel ruled no breach of Clauses 7.2 and 7.8 of the Code.

2 Claims and main imagery

COMPLAINT

The Alliance alleged that the claim **'**Change the course of treatment by reducing CV risk' promoted Victoza's additional CV benefits as the primary reason to prescribe. This call to action was misleading and inconsistent with the SPC as it put undue emphasis on CV benefits observed in a clinical trial.

The Alliance noted that the main imagery of the exhibition panel depicted a pavement, adjacent to which was a wall with the word 'HbA1CV'. A woman (presumably a type 2 diabetic) was walking down a shaded pavement, marked by HbA1c, about to turn a corner into the light part of the pavement marked CV. This suggested that Victoza's added benefits with respect to CV risk were at least equally important as the licensed indication, which was glycaemic control of HbA1c. Together with the above claim, the Alliance alleged that this was misleading, inconsistent with the SPC and thus in breach of Clauses 3.2, 7.2 and 7.8.

RESPONSE

Novo Nordisk submitted that the claim 'Change the course of treatment by reducing CV risk' did not promote the CV benefits of Victoza as the primary reason to prescribe. It was within the context of treating type 2 diabetes in patients suitable for Victoza (in line with the indication). The claim encouraged health professionals to consider CV risk reduction as part of the treatment goal for patients with type 2 diabetes.

As explained at point 1 above, the licensed indication for Victoza was no longer glycaemic control of HbA1c, as stated by the Alliance, it was 'treatment of adults with insufficiently controlled type 2 diabetes mellitus...'. Therefore, it was entirely reasonable to encourage consideration of a more holistic approach to adult type 2 diabetes treatment. This was consistent with the National Institute for Health and Care Excellence (NICE) guidelines for treatment of adults with type 2 diabetes, the Scottish Intercollegiate Guidelines Network (SIGN) 154 guideline, as well as the Victoza SPC.

Novo Nordisk submitted that the promotional claims and imagery used on the exhibition panel were not misleading or inconsistent with the Victoza SPC and hence not in breach of Clauses 3.2, 7.2 or 7.8.

PANEL RULING

The Panel noted its ruling in point 1 above. The major inclusion criteria for the LEADER trial were type 2 diabetes patients aged 50 or more with at least one cardiovascular coexisting condition or aged 60 years or more with at least one cardiovascular risk factor.

The LEADER trial showed that Victoza was superior to placebo in preventing MACE (major adverse cardiovascular events (CV death, non fatal myocardial infarction or non-fatal stroke). It also significantly reduced the rist of expanded MACE (primary MACE, unstable angina pectoris leading to hospitalisation, coronary revasculation or hospitalisation due to heart failure).

The Panel considered that the important factor was that the patient had type 2 diabetes. The outcome of the CV study would be of interest to those that treated type 2 diabetes. There was a change in the Victoza SPC and the company was fully entitled to draw attention to that change. The benefits shown in the LEADER trial were in relation to high cardiovascular risk patients. The Victoza SPC also referred to more general information in that, a post hoc analysis of serious major adverse cardiovascular events (cardiovascular death, myocardial infarction, stroke) from intermediate and long term phase 2 and 3 trials showed no increase in CV risk for liraglutide versus all comparators.

The Panel considered that the claim 'Change the course of treatment by reducing CV risk' in conjunction with 'HbA1CV' emphasised the CV risk reduction with Victoza. However the context of the claims was important and needed to be considered as did the audience. The frame part of the stand referred to a qualifcation, 'In adults with type 2 diabetes and high CV risk...'. Given its ruling in point 1 above and taking all the circumstances into account the Panel did not consider that Novo Nordisk was promoting the additional CV benefits as the primary reason to prescribe Victoza as alleged. In the Panel's view the mention of the CV benefits was not misleading or inconsistent with the SPC as alleged. The Panel ruled no breach of Clause 3.2. The stand was not misleading in this regard and no breach of Clauses 7.2 and 7.8 were ruled.

3 Conduct of inter-company dialogue

COMPLAINT

The Alliance alleged that given the position taken by Novo Nordisk during inter-company dialogue, Novo Nordisk had failed to maintain high standards and reduced confidence in the industry, in breach of Clause 9.1.

The Alliance explained that it initiated inter-company dialogue with Novo Nordisk by letter on 27 November 2017, to complain about a Victoza leavepiece (ref UK/VT/0717/0463) (copy provided). The Alliance alleged that the leavepiece breached the Code in several ways and noted eight aspects of concern. The primary concern was that the overall promotional content, the headline claims and the imagery were inconsistent with Victoza's indication for use and the additional benefits of treatment as reflected in section 5 of the SPC. This put excessive promotional emphasis on the additional CV benefits of the medicine and promoted these as the primary reason to prescribe.

Novo Nordisk replied on 11 December 2017 and stated that it believed the leavepiece complied with the Code and suggested an inter-company teleconference. The teleconference on 19 December 2017 resulted in no agreement or resolution on any aspect discussed. On 4 January 2018, Novo Nordisk wrote to the Alliance to state that it thought the leavepiece was compliant but that 'to avoid any misperceptions' it had decided to withdraw it and that when relevant, it

would take the comments from the Alliance into consideration in respect of other assets and when drafting new materials.

The Alliance stated, however, that it was concerned that Novo Nordisk had other similar promotional materials in circulation and so on 10 January it asked Novo Nordisk to withdraw those materials. In reply on 22 January, Novo Nordisk stated that it had re-examined all materials and all complied with the Code; it added that 'no further withdrawal was needed,' and that it would take the Alliance's comments 'into consideration for future materials or activities for Victoza'. The Alliance sought clarity on 29 January and Novo Nordisk replied on 7 February that it 'did not confirm that there are no other materials in circulation to which some aspects identified in the leave piece may refer.'

The Alliance wrote on 15 February 2018 to notify Novo Nordisk that it did not 'consider this matter closed in relation to any other materials affected by the aspects we have raised' and that 'should the Alliance become aware of any further promotional materials affected by any of the aspects raised in the original withdrawn leave piece, we would refer the matter directly to the PMCPA.'

The Alliance alleged that Novo Nordisk's promotional stand for Victoza at the Diabetes UK Professional Conference on 13 March 2018 demonstrated that it continued to promote Victoza in the manner complained about in inter-company dialogue.

RESPONSE

Novo Nordisk stated that it took its responsibility to resolve any complaints through inter-company dialogue extremely seriously and it was disappointed that this matter was unable to be resolved with the Alliance directly. Novo Nordisk stated that it entered into inter-company dialogue with a willingness to discuss the concerns raised by the Alliance.

As a result of the discussions, Novo Nordisk withdrew the leavepiece at issue without prejudice and agreed to re-examine current promotional materials based on the discussions in the inter-company dialogue. As a result of this, the exhibition panel used at the Diabetes UK Professional Conference was created with even more explicit prominence of the licensed indication of Victoza. For the avoidance of doubt, Novo Nordisk stated that it made it clear that it did not confirm that there were no other materials in circulation to which some aspects identified in the leavepiece might refer (letter to the Alliance 7 February 2018). Novo Nordisk stated that it did not agree with the Alliance's concerns about the claims in the leavepiece and so it did not withdraw all materials as requested.

Novo Nordisk stated that it fully engaged in inter-company dialogue and was transparent about not adapting some claims and the imagery as it considered these complied with the Code. Novo Nordisk submitted that it had upheld high standards and hence was not in breach of Clause 9.1.

PANEL RULING

The Panel noted the important role of inter-company dialogue. Novo Nordisk had withdrawn the leavepiece without prejudice. The Panel noted that there were similarities between the leavepiece at issue in the inter-company dialogue and the exhibition stand the subject of points 1 and 2 above. However Novo Nordisk had not agreed with The Alliance's view that the leavepiece was in breach of the Code. It was disappointing that Novo Nordisk had not given

The Alliance more details. Novo Nordisk's letter of 4 January stated that the company now considered the inter-company matter resolved. In the light of the content of the exhibition stand it appeared that The Alliance considered that the inter-company matter was not resolved. The Panel appreciated the frustration for companies when issues raised and considered resolved at inter-company level appeared again in a different format. The main difference with the photograph of the women turning the corner related to the claim 'In adults with type 2 diabetes' used in the leavepiece had been amended to 'In adults with insufficiently controlled type 2 diabetes; in the exhibition stand. The Panel considered that there were differences in the leavepiece and the exhibition stand. It did not accept that Novo Nordisk failed to maintain high standards as alleged and ruled no breach of Clause 9.1.

Complaint received **23 April 2018**

Case completed **28 August 2018**