CASE AUTH/3543/7/21

NOVO NORDISK v ELI LILLY

Promotion of Trulicity (dulaglutide)

Novo Nordisk submitted a complaint about Eli Lilly regarding the promotion of Trulicity (dulaglutide) in a presentation entitled 'Barber's Box comparison of GLP-1 receptor agonists'. Whilst the case was received in August 2020, in error it was not processed until July 2021.

Novo Nordisk stated that the Barber's Box presentation was promotional and was aimed at health professionals treating patients with type 2 diabetes. According to Novo Nordisk the presentation was designed to compare GLP-1 receptor agonists (GLP-1RAs); specifically, Lilly's dulaglutide (Trulicity) with Novo Nordisk's liraglutide (Victoza) and semaglutide (Ozempic).

Novo Nordisk explained that each GLP-1 receptor agonist had a corresponding cardiovascular outcome trial (CVOT); the REWIND trial assessed dulaglutide, LEADER assessed liraglutide and SUSTAIN-6 assessed semaglutide. Each CVOT compared the respective product to placebo; there was no CVOT head-to-head data directly comparing any of these products. CVOTs in diabetes had certain similarities and differences, hence any indirect comparison between them was confounded by a trial's population, definitions and criteria as well as the phase of the development of the medicine.

Novo Nordisk's concerns with the presentation were as follows:

1 Alleged selective comparison between products, resulting in misleading and unsubstantiated claims

Novo Nordisk alleged that Lilly was using the Barber's Box framework to compare and promote dulaglutide compared to semaglutide and liraglutide by cherry picking sections of the summary of product characteristics (SPCs) and very selected data sets from various publications. Ambiguous and unsubstantiated conclusions and claims were drawn from this selected information and presented visually through shading of boxes throughout the presentation wherein one product was depicted as 'favourable' over another. For example, weight and glucose lowering efficacy conclusions from the direct head-to-head data of SUSTAIN 7 were combined with selective indirect comparisons between REWIND and SUSTAIN 6 sub-population cardiovascular data to conclude a subjective degree of shading on Slide 22 of the presentation. The overall weight of such selective comparison would conclude a subjective favourability for dulaglutide.

In the section where dulaglutide was compared to liraglutide, there was no reference to data or publications and therefore no substantiation at all for the shading of the boxes.

Novo Nordisk alleged that the manner and degree to which Lilly had chosen to shade each box throughout the presentation misled a health professional to draw a conclusion

that the data related to all patients with type 2 diabetes, it was not transparent that differing data sources and data sets within those sources had been used.

2 Alleged undue emphasis on trial sub-populations to draw indirect comparisons between trials

Novo Nordisk stated that the presentation drew comparisons between trials and promoted an advantage of dulaglutide over semaglutide by highlighting a selected sub-group (patients without established cardiovascular disease) from the two CVOTs (REWIND and SUSTAIN 6). Both trials were designed and powered to demonstrate potential differences in Major Adverse Cardiovascular Events (MACE) as a composite primary endpoint for the full trial population (a blended at-risk population). Any subgroup sensitivity analysed were to demonstrate heterogeneity of the primary composite outcome. Neither product showed a statistically significant cardiovascular outcome benefit in this sub-population. An isolated, selected quote was taken from the updated 2019 American Diabetes Association and European Association for the Study of Diabetes (ADA/EASD) consensus report (Buse J et al 2020) which gave undue emphasis to this sub-population data. Whilst the ADA/EASD consensus report mentioned that the level of evidence in this sub-population group was strongest for dulaglutide, it also stated that dulaglutide did not achieve statistical significance in this sub-population. Furthermore, the report highlighted that the other GLP-1RA CVOTs included fewer participants in this sub-population and therefore it was currently unknown if the numerical benefit seen in REWIND was due to the therapy or differences between the GLP-1RA CVOT designs. This latter statement from the report was omitted from the presentation. The overall guidance of the ADA/EASD consensus was that any GLP-1RA with a label indication for reducing cardiovascular disease (CVD) events should be considered. The label indications for the two products (reflected in the SPCs) were exactly the same. The Lilly presentation did not adequately reflect the full statement in the ADA/EASD guideline.

Furthermore, other relevant international guidelines equally recommended dulaglutide, liraglutide and semaglutide in patients with high/very high risk of CVD and classified the level of evidence for all agents to be the same. This was not included in the presentation.

In addition, an isolated statement was taken from the semaglutide European Medicines Agency (EMA) regulatory report and placed directly opposite a quote from the ADA Standards publication, rather than a comparable reference of the dulaglutide EMA assessment, again selectively cherry picking and showing selected data rather than the comparable dataset.

Novo Nordisk stated that it had the same concerns regarding the inappropriate indirect comparisons between the LEADER and REWIND trials which resulted in an ambiguous efficacy conclusion.

3 Alleged cherry picking of data resulting in misleading and unbalanced presentation and conclusions

Novo Nordisk alleged that, as described above, only very selected statements pertaining to the ADA/EASD consensus report had been included thus not adequately reflecting the guidance. The presentation did not include the summary tables or algorithms of the ADA/EASD consensus report but rather cherry picked one selected statement. There were other equally strong quotes from the original report in favour of semaglutide which were relevant and yet not presented.

Novo Nordisk alleged that Lilly had chosen to highlight one favourable difference between the semaglutide and dulaglutide SPCs, that of diabetic retinopathy, and yet there were many other relevant differences within the SPCs when evaluating which product to prescribe according to this framework. In addition, for the patient considerations aspect of the framework, an important consideration could be that only one semaglutide pen was needed per month whilst four pens were required if using dulaglutide.

In conclusion, Novo Nordisk alleged that Lilly was using the presentation and the guise of the 'Barber framework' to pick and choose which data to focus and highlight from various publications and product SPCs, to present unsubstantiated, ambiguous conclusions and claims. The presentation repeatedly failed to provide sufficient information and was misleading. Additionally, the principle to use a subjective comparative framework to denote differentiation between products and make favourable claims was concerning and Novo Nordisk therefore concluded that this was a failure to maintain high standards.

The detailed response from Eli Lilly is given below.

The Panel noted that the presentation at issue was titled 'Barber's Box comparison of GLP-1 receptor agonists'. The Panel noted Lilly's explanation that the 'Barber's Box' framework was derived from the principles outlined in Nick Barber's 1995 BMJ publication which proposed four aims (efficacy, safety and tolerability, cost and patient factors) that a prescriber should consider when prescribing and monitoring a medicine to be used as an aid for discussion and decision making. The Panel noted Lilly's submission that the approach included all the key attributes that formulary committees and health professionals would consider in their decision making. The Panel further noted Lilly's submission that this approach ensured complete balance in comparison of therapies by highlighting all key attributes, including those where comparison with its product dulaglutide clearly favoured competitor products. The colouring of each component of the 'Barber's Box' was designed to reflect how the therapies compared when considering all relevant aspects of an attribute, which might include generalisability of study data or requirements for specific safety monitoring.

1 Alleged selective comparison between products, resulting in misleading and unsubstantiated claims

Overall, the Panel considered that the presentation contained little information about the Barber's Box nor were relevant caveats presented in the slides to enable the audience to know how much weight to attach to the shaded Barber's Boxes including at Slides 22, 31 and 34. This was particularly important given the gradations of shading within the comparative efficacy boxes which the Panel considered audiences would necessarily, in

the absence of any quantitative information and caveats on the slides, interpret differently. The Panel considered that the failure to provide sufficient information, such as relevant caveats on the shaded slides in question, meant that the presentation was misleading and the implications of the shaded comparative efficacy box were incapable of substantiation. Breaches of the Code were ruled.

The Panel noted that, contrary to Novo Nordisk's allegation, Slide 22 showed that efficacy favoured semaglutide. On this very narrow ground, the Panel did not consider that the shading of the efficacy section of the Barber's box on Slide 22 misleadingly implied a subjective favourability for dulaglutide as alleged and based on the narrow allegation, no breaches of the Code were ruled.

The Panel noted that Slides 31 and 34 included the Barber's Box comparison of dulaglutide 1.5mg and liraglutide 1.8mg. The Efficacy and Safety/Tolerability box were referenced to Dungan et al 2014 and the Cost box to MIMS. The Panel therefore did not consider that Novo Nordisk had established that there was no reference to data or publications and therefore no substantiation at all for the shading of the boxes as alleged and based on the very narrow allegation no breach of the Code was ruled.

2 Alleged undue emphasis on trial sub-populations to draw indirect comparisons between trials

The Panel noted that it appeared from the complaint that this allegation was in relation to Slide 21 which was titled 'Efficacy: Cardiovascular Outcome Trials'. The slide included a forest plot representing results of Events/patients (%) for dulaglutide vs placebo for patients with established CVD and no established CVD from the REWIND trial. Next to this was a similar forest plot representing results for semaglutide vs placebo from the SUSTAIN-6 trial. To the right of these forest plots it stated in a prominent highlighted box '2019 Update to ADA/EASD Consensus Report "...the level of evidence to support the use of GLP-1 receptor agonists for the primary prevention is strongest for dulaglutide but lacking for other GLP-1 receptor agonists"'.

The forest plot relating to REWIND showed favourability for dulaglutide vs placebo overall and in the subgroups of patients with and without established CVD. Below the forest plot it stated 'ADA Standards in Medical Care for Diabetes...there was consistent benefit in the dulaglutide trial in patients with and without established ASCVD'.

The forest plot relating to SUSTAIN-6 showed favourability for semaglutide vs placebo overall and in the subgroup of patients with established CVD vs placebo but showed no difference in the subgroup without established cardiovascular disease. Below this forest plot it stated 'EMA Assessment Report". In [the] CVOT a number of subjects were included with risk factors "only". In these subjects, no effect on MACE was seen, but the numbers were too small to draw firm conclusions"'.

The Panel considered that the presentation of the CVOT outcomes on Slide 21 and inclusion of selected statements from the 2019 Update to the ADA/EASD Consensus Report and the ADA Standards in Medical Care for Diabetes and EMA Assessment Report, without reference to the lack of statistical significance achieved in the REWIND sub-group population without established CVD and the failure to highlight that it was currently unknown whether the numerical benefit seen in REWIND was due to the

therapy or differences between the GLP-1RA CVOT designs, implied an advantage of dulaglutide over semaglutide which was misleading and incapable of substantiation and breaches of the Code were ruled.

On the evidence before it, the Panel considered that the presentation of the trial outcomes on Slide 33 and inclusion of the statements from the 2019 Update to the ADA/EASD Consensus Report and the ADA Standards in Medical Care for Diabetes and EMA Assessment Report, without reference to the lack of statistical significance achieved in the REWIND sub-group population without established CVD and the failure to highlight that it was currently unknown if the numerical benefit seen in REWIND was due to the therapy or differences between the GLP-1RA CVOT designs, implied an advantage of dulaglutide over liraglutide which was misleading and incapable of substantiation and breaches of the Code were ruled.

3 Cherry picking of data resulting in misleading and unbalanced presentation and conclusions

The Panel noted that, in addition to Novo Nordisk's concern that only selected statements pertaining to the ADA/EASD consensus report had been included which was covered at Point 2, Novo Nordisk further alleged that there were other equally strong quotes from the original report in favour of semaglutide which were relevant and yet not presented. The example given was 'GLP-1 receptor agonists have high glucose-lowering efficacy, but with variation within the drug class. Evidence suggests that the effect may be greatest for semaglutide once weekly, followed by dulaglutide and liraglutide'. The Panel noted Lilly's submission that including this statement would be superfluous given that Lilly presented the glucose lowering data from SUSTAIN 7 and AWARD 6, making it clear that injectable semaglutide had greater glucose lowering than dulaglutide and that dulaglutide and liraglutide had similar glucose lowering effect. The Panel noted that whilst AWARD-6 was not referred to within the presentation in question, Slide 19 was titled 'Efficacy: SUSTAIN 7' and included a graph from SUSTAIN 7 showing the change from baseline (%) of HbA1c for semaglutide 0.5mg and 1.0mg vs dulaglutide 0.75mg and 1.5mg respectively which showed that at low and high doses, semaglutide was superior to dulaglutide in improving glycaemic control. The Panel did not consider that Novo Nordisk had established that failing to refer to the quote 'GLP-1 receptor agonists have high glucose-lowering efficacy, but with variation within the drug class. Evidence suggests that the effect may be greatest for semaglutide once weekly, followed by dulaglutide and liraglutide' from the ADA/EASD Consensus Report was misleading as alleged and no breaches of the Code were ruled.

The Panel noted Novo Nordisk's further allegation that Lilly had chosen to highlight one favourable difference between the semaglutide and dulaglutide SPCs, that of diabetic retinopathy yet there were many other relevant differences within the SPCs when evaluating which product to prescribe according to this framework. In this regard, the Panel noted Novo Nordisk's submission that another important safety consideration could be that the dulaglutide SPC highlighted atrioventricular block and sinus tachycardia as common whilst for semaglutide increased heart rate was listed as uncommon. In addition, for the patient considerations aspect of the framework, an important consideration could be that only one semaglutide pen was needed per month whilst four pens were required if using dulaglutide.

The Panel noted that Slide 24 was headed 'Safety/tolerability: Additional monitoring considerations for patients with diabetic retinopathy and treated with insulin'. It included a bar graph showing the share of GLP-1RA prescribing in combination with insulins stated that the prevalence of diabetic retinopathy in people with type 2 diabetes was in the order of 25.2% and included a grey box on the left-hand side of the slide which stated 'Semaglutide SmPC: Caution should be exercised when using semaglutide in patients with diabetic retinopathy treated with insulin. These patients should be monitored closely and treated according to clinical guidelines'. The Panel noted that Section 4.4 of the Ozempic (semaglutide) SPC stated beneath the heading 'Diabetic retinopathy', 'In patients with diabetic retinopathy treated with insulin and semaglutide, an increased risk of developing diabetic retinopathy complications has been observed (See section 4.8). Caution should be exercised when using semaglutide in patients with diabetic retinopathy treated with insulin. These patients should be monitored closely and treated according to clinical guidelines. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded'. The Panel noted Lilly's submission that none of the other five GLP-1 RAs marketed in the UK had this precautionary language in their SPCs.

The Panel noted that it appeared that the only head-to-head study between semaglutide and dulaglutide was SUSTAIN 7, a randomised, open-label, phase 3b trial comparing semaglutide versus dulaglutide once weekly in patients with type 2 diabetes, in which adverse events of diabetic retinopathy were reported by two patients (1%) receiving semaglutide 0·5mg, two patients (1%) receiving dulaglutide 0·75 mg, two patients (1%) receiving semaglutide 1·0 mg, and three patients (1%) receiving dulaglutide 1·5 mg.

The Panel noted Novo Nordisk's submission that throughout the course of inter-company dialogue, Lilly had refused to include the relevant, available, robust, phase 3a head-to-head data (SUSTAIN 7 and AWARD 6) pertaining to safety data and patient reported outcomes between the products being compared including the head-to-head retinopathy data from SUSTAIN 7. In this regard, the Panel noted that whilst AWARD-6 was not referred to within the presentation before it, Slide 23 was titled 'Safety/tolerability: SUSTAIN 7 adverse events (extract)'; diabetic retinopathy, however, was not referred to.

The Panel further noted Lilly's submission that patient reported outcomes from SUSTAIN 7 and AWARD 6 did not evaluate patient preference, as they were parallel-group (as opposed to crossover) studies that did not allow patients to directly compare any attributes of the therapies, including injection devices and dose-titration regimens, with each other.

The Panel further noted that Lilly disagreed that the well-known class effect of tachycardia was remotely like the warning language for semaglutide regarding the risk of diabetic retinopathy complications. Low grade tachycardia, whether common or less common, occurred with all the GLP-1 RAs as an adverse reaction, and all the GLP-1 RAs studied in CVOTs have been shown to be at least safe from a CV risk perspective and in some cases, such as REWIND, LEADER and SUSTAIN 6, to provide CV benefit, despite tachycardia. In contrast, complications of diabetic retinopathy were clearly very serious and potentially life changing. Novo Nordisk argued that the SUSTAIN 7 retinopathy data was relevant to the discussion, but as the semaglutide SPC stated, 'Systematic evaluation of diabetic retinopathy complications was only performed in the

cardiovascular outcomes trial' (SUSTAIN 6), which was a 2-year clinical trial investigating 3,297 patients with type 2 diabetes. The Panel noted Novo Nordisk's submission that the slide on monitoring considerations for patients with diabetic retinopathy and treated with insulin was not intended to be a risk analysis of either therapy regarding diabetic retinopathy. Those risk analyses had already been conducted, as they should be, by the EMA. The slide simply reflected a requirement for semaglutide in its SPC that did not exist for dulaglutide, conveying a key difference in monitoring requirements between these two agents and therefore an advantage for dulaglutide in that specific context.

Lilly stated that it did not understand Novo Nordisk's point about the different number of pens required per month being relevant to patient considerations, as they had presented neither arguments nor data to support why one pen per month would be an advantage for patients compared with four pens.

Whilst in the Panel's view it was clear that the statement 'Caution should be exercised when using semaglutide in patients with diabetic retinopathy treated with insulin. These patients should be monitored closely and treated according to clinical guidelines' on Slide 24 was taken from the semaglutide SPC, the Panel noted that Slide 18 included 'Patients with diabetic retinopathy and treated with insulin' as an example of an advantage for dulaglutide in several clinical contexts.

Nonetheless, the Panel did not consider that inclusion of the statement from the semaglutide SPC with regard to diabetic retinopathy without referring to atrioventricular block and sinus tachycardia as being common for dulaglutide and increased heart rate as being uncommon for semaglutide was misleading as alleged or did not reflect the available evidence with regard to adverse reactions and based on the complainant's narrow allegation, no breaches of the Code were ruled.

Nor did the Panel consider that Novo Nordisk had provided evidence to establish, on the balance of probabilities, that failure to mention that only one semaglutide pen was needed per month whilst four pens were required if using dulaglutide was an important factor for the patient considerations aspect of the framework was misleading as alleged. No breaches of the Code were ruled.

The Panel noted Novo Nordisk's allegation that despite agreeing during a previous inter-company dialogue that indirect CVOT comparisons should not be made, Lilly continued to do so within this presentation. Additionally, the principle to use a subjective comparative framework to denote differentiation between products and make favourable claims was concerning and Novo Nordisk therefore concluded that this was a failure to maintain high standards.

In relation to the allegation that in principle to use a subjective comparative framework to denote differentiation between products and make favourable claims was concerning, the Panel did not consider that, in principle, it was necessarily unacceptable to use the Barber's Box framework so long as its presentation complied with the Code. The Panel therefore did not consider that Novo Nordisk had established that, in principle, using the Barber's Box framework in itself meant that Lilly had failed to maintain high standards and based on Novo Nordisk's narrow allegation on this point, no breach of the Code was ruled.

The Panel noted the parties' submissions regarding inter-company dialogue and the presentation of CVOT data.

The Panel noted that the slide deck in question was retired on 26 March 2020 and did not consider that Novo Nordisk had established, on the balance of probabilities, that despite agreeing during a previous inter-company dialogue that indirect CVOT comparisons should not be made, Lilly continued to do so within the Barber's Box presentation at issue. All of the inter-company dialogue post-dated the presentation at issue. No breach of the Code was ruled in this regard.

Novo Nordisk Ltd submitted a complaint about Eli Lilly and Company Limited regarding the promotion of Trulicity (dulaglutide) in a presentation entitled 'Barber's Box comparison of GLP-1 receptor agonists' (PP-DG-GB-0573 January 2020). Whilst the case was received in August 2020, in error it was not processed until July 2021.

On reviewing Novo Nordisk's complaint, the Case Preparation Manager was not satisfied that inter-company dialogue proved unsuccessful. This decision was, at the request of Novo Nordisk, referred to an independent referee who decided that inter-company dialogue was unsuccessful.

COMPLAINT

Background

Novo Nordisk stated that the Barber's Box presentation was promotional and was aimed at health professionals treating patients with type 2 diabetes. The presentation was designed to compare GLP-1 receptor agonists (GLP-1RAs); specifically, Lilly's dulaglutide (Trulicity) with Novo Nordisk's liraglutide (Victoza) and semaglutide (Ozempic) once weekly (ow).

All three GLP-1 receptor agonists were indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:

- as monotherapy when metformin was considered inappropriate due to intolerance or contraindications
- in addition to other medicinal products for the treatment of diabetes.

Each GLP-1 receptor agonist had a corresponding cardiovascular outcome trial (CVOT); the REWIND trial assessed dulaglutide (Gerstein HC *et al* 2019), LEADER assessed liraglutide (Marso SP *et al* 2016) and SUSTAIN-6 assessed semaglutide (Marso SP *et al* 2016). Each of these CVOTs compared the respective product to placebo; there was no CVOT head-to-head data directly comparing any of these products. Cardiovascular outcomes trials in diabetes had certain similarities and differences, hence any indirect comparison between them was confounded by a trial's population, definitions and criteria as well as the phase of the development of the medicine.

Direct head-to-head, randomised controlled efficacy trials compared these products:

- SUSTAIN 7 (Pratley R *et al* 2018): compared dulaglutide to semaglutide ow
- AWARD 6 (Dungan K *et al* 2014): compared dulaglutide to liraglutide.

The presentation also referenced a paper published in the British Medical Journal in 1995 entitled 'What constitutes good prescribing?' (Barber T 1995). In the publication, Barber proposed four aims which a prescriber should try to achieve when prescribing and monitoring a medicine to be used as an aid for discussion and decision making. The presentation tried to utilise the four aims, ie the Barber's Box framework.

1 Alleged selective comparison between products, resulting in misleading and unsubstantiated claims

Novo Nordisk alleged that Lilly was using the Barber's Box framework to compare and promote dulaglutide compared to semaglutide and liraglutide by cherry picking sections of the summary of product characteristics (SPCs) and very selected data sets from various publications. Ambiguous and unsubstantiated conclusions and claims were drawn by Lilly from this selected information and presented visually through shading of boxes throughout the presentation wherein one product was depicted as 'favourable' over another. For example, weight and glucose lowering efficacy conclusions from the direct head-to-head data of SUSTAIN 7 were combined with selective indirect comparisons between REWIND and SUSTAIN 6 sub-population cardiovascular data to conclude a subjective degree of shading on Slide 22 of the presentation. The overall weight of such selective comparison would conclude a subjective favourability for dulaglutide.

In the section where dulaglutide was compared to liraglutide, there was no reference to data or publications and therefore no substantiation at all for the shading of the boxes.

The manner and degree to which Lilly had chosen to shade each box throughout the presentation and the resulting strong conclusions and claims drawn between the products was subjective, and not substantiated by any peer review publication, health technology or regulatory assessment. It misled a health professional to draw a conclusion that the data related to all patients with type 2 diabetes, it was not transparent that differing data sources and data sets within those sources had been used.

This presentation drew strong conclusions and claims which were not accurate or capable of substantiation and as a result were misleading.

2 Alleged undue emphasis on trial sub-populations to draw indirect comparisons between trials

Novo Nordisk stated that within the presentation, Lilly drew comparisons between trials and promoted an advantage of dulaglutide over semaglutide by highlighting a selected sub-group (patients without established cardiovascular disease) from the two CVOTs (REWIND and SUSTAIN 6 trials). Both trials were designed and powered to demonstrate potential differences in Major Adverse Cardiovascular Events (MACE) as a composite primary endpoint for the full trial population (a blended at-risk population). Any subgroup sensitivity analysed were to demonstrate heterogeneity of the primary composite outcome. Neither product showed a statistically significant cardiovascular outcome benefit in this sub-population. An isolated, selected quote was taken from the updated 2019 American Diabetes Association and European Association for the Study of Diabetes (ADA/EASD) consensus report (Buse J *et al* 2020) which gave undue emphasis to this sub-population data. Whilst the ADA/EASD consensus report mentioned that the level of evidence in this sub-population group was strongest for dulaglutide, it also stated that dulaglutide did not achieve statistical significance in this sub-population.

Furthermore, the report highlighted that the other GLP-1RA CVOTs included fewer participants in this sub-population and therefore it was currently unknown if the numerical benefit seen in REWIND was due to the therapy or differences between the GLP-1RA CVOT designs. This latter statement from the report was omitted from the presentation. The overall guidance of the ADA/EASD consensus was that any GLP-1RA with a label indication for reducing cardiovascular disease (CVD) events should be considered (figure 1 and the bolded text on page 5). As stated above, the label indications for the two products (reflected in the SPCs) were exactly the same. The Lilly presentation did not adequately reflect the full statement in the ADA/EASD guideline.

Furthermore, other relevant international guidelines such as 2019 European Society of Cardiology Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD equally recommended dulaglutide, liraglutide and semaglutide in patients with high/very high risk of CVD and classified the level of evidence for all agents to be the same (page 298). This was not included in the presentation.

In addition, an isolated statement was taken from the semaglutide European Medicines Agency (EMA) regulatory report and placed directly opposite a quote from the ADA Standards publication, rather than a comparable reference of the dulaglutide EMA assessment, again selectively cherry picking and showing selected data rather than the comparable dataset.

Novo Nordisk stated that it had the same concerns regarding the inappropriate indirect comparisons between the LEADER and REWIND trials presented in Slides 32 and 33 which resulted in an ambiguous efficacy conclusion on Slide 34 of the presentation.

During a previous, separate inter-company dialogue, which also pertained to the presentation of the REWIND CVOT data (concluded March 2020), Lilly agreed that outcome data between the diabetes CVOTs should not be compared directly due to differences in trial designs and conduct and that audiences should not be misled regarding the lack of statistical significance achieved in the REWIND cardiovascular sub-group populations. Despite this, Lilly continued to promote an advantage of dulaglutide over semaglutide and liraglutide based on indirect comparisons from data of the respective CVOTs.

3 Alleged cherry picking of data resulting in misleading and unbalanced presentation and conclusions

Novo Nordisk alleged that, as described above, only very selected statements pertaining to the ADA/EASD consensus report had been included thus not adequately reflecting the guidance. The presentation did not include the summary tables or algorithms of the ADA/EASD consensus report but rather cherry picked one selected statement. There were other equally strong quotes from the original report in favour of semaglutide which were relevant and yet not presented, for example: ‘GLP-1 receptor agonists have high glucose-lowering efficacy, but with variation within the drug class. Evidence suggests that the effect may be greatest for semaglutide once weekly, followed by dulaglutide and liraglutide’ (Davies *et al* 2018).

Novo Nordisk stated that throughout the course of the inter-company dialogue, Lilly had refused to include the relevant, available, robust, phase 3a head-to-head data (SUSTAIN 7 and AWARD 6) pertaining to safety data and patient reported outcomes between the products being compared. When requested to represent the head-to-head retinopathy data from SUSTAIN 7, Lilly responded that this was not necessary and the point of the Barber’s Box was to draw out

meaningful differences between therapies. Lilly had chosen to highlight one favourable difference between the semaglutide and dulaglutide SPC, that of diabetic retinopathy, and yet there were many other relevant differences within the SPCs when evaluating which product to prescribe according to this framework. For example, another important safety consideration could be that the dulaglutide SPC highlighted atrioventricular block and sinus tachycardia as common, whilst for semaglutide increased heart rate was listed as uncommon. In addition, for the patient considerations aspect of the framework, an important consideration could be that only one semaglutide pen was needed per month whilst four pens were required if using dulaglutide.

Novo Nordisk's concerns about the overall weight and balance as a principle to promotion of dulaglutide was again shared in the last inter-company dialogue and remained unresolved as many discussion points were viewed differently between the two companies.

Conclusion

Novo Nordisk alleged that Lilly was using the presentation and the guise of the 'Barber framework' to pick and choose which data to focus and highlight from various publications and product SPCs, to present unsubstantiated, ambiguous conclusions and claims. The presentation repeatedly failed to provide sufficient information and was misleading. Therefore, Novo Nordisk alleged a breach of Clauses 7.2, 7.3, 7.4, 7.8 and 7.9 of the 2019 Code. On the subject of cardiovascular outcomes trials, despite agreeing during a previous inter-company dialogue that indirect CVOT comparisons should not be made, Lilly continued to do so within this presentation. Additionally, the principle to use a subjective comparative framework to denote differentiation between products and make favourable claims was concerning and Novo Nordisk therefore concluded that this was a failure to maintain high standards and a breach of Clause 9.1.

RESPONSE

Lilly stated that it was committed to resolving this complaint through inter-company dialogue and took every reasonable step to do so. Lilly made a detailed submission about inter-company dialogue.

Lilly disagreed with Novo Nordisk's allegations that the 'Barber's Box' approach Lilly had taken was in breach of Clauses 7.2, 7.3, 7.4, 7.8, 7.9 and 9.1 of the Code. The information provided was accurate, fair and balanced, and was not misleading, and all claims were fully referenced to appropriate sources of authority and capable of substantiation.

Lilly addressed the assertions made by Novo Nordisk in turn.

1 Selective comparison between products, resulting in misleading and unsubstantiated claims

Lilly stated that Novo Nordisk was essentially challenging the appropriateness of the 'Barber's Box' comparative framework Lilly had used.

Lilly stated that as it outlined in its responses to Novo Nordisk's initial complaint, the 'Barber's Box' was a framework that was derived from the principles outlined in Nick Barber's 1995 BMJ publication (nowhere did the publication use the term 'Barber's Box'), with evolution of the

framework over time as appropriate. The comprehensive, evidence-based, fully referenced approach was considered by health professionals – through consistent positive feedback in response to the presentations – to exemplify a fair and balanced approach, as it included all the key attributes (efficacy, safety and tolerability, cost and patient factors) that formulary committees and health professionals would consider in their decision making. This approach ensured complete balance in comparison of therapies by highlighting all key attributes, including those where comparison with its product dulaglutide clearly favoured competitor products. The colouring of each component of the 'Barber's Box' was designed to be reflective of how the therapies compared when considering all relevant aspects of an attribute, which might include generalisability of study data or requirements for specific safety monitoring. All aspects of the analysis that led to the shading for each section of the 'Barber's Box' were detailed both in the slides and hence to the audience and the colour shading was thus not seen in isolation but was always contextualised by the preceding analyses.

Lilly stated that Novo Nordisk's claim that Lilly had 'cherry-picked' attributes and data sets, was a curious claim given that Lilly had been so comprehensive in its selection, including attributes and data sets that clearly favoured Novo Nordisk's products.

The example Novo Nordisk gave to support its allegation that Lilly was drawing inappropriately favourable conclusions for dulaglutide refuted Novo Nordisk's own argument, as detailed in the paragraph below. Novo Nordisk stated, 'For example weight and glucose lowering efficacy conclusions from the direct head-to-head data of SUSTAIN 7 were combined with selective indirect comparisons between REWIND and SUSTAIN 6 sub-population cardiovascular data to conclude a subjective degree of shading on Slide 22 of the presentation. The overall weight of such selective comparison would conclude a subjective favourability for dulagltuide (sic)'.

Firstly, Lilly stated that the balance imposed by use of the 'Barber's Box' framework was powerfully illustrated by the fact that Lilly presented the SUSTAIN 7 study at all, given that it was a Novo Nordisk sponsored study that demonstrated superiority of Novo Nordisk's product semaglutide over Lilly's product dulaglutide for both glucose lowering and weight loss, two of the key efficacy considerations in treatment of type 2 diabetes. Secondly, as Lilly outlined in its response to Novo Nordisk's initial complaint, the conclusions, based on analysis of the data, were objective. Semaglutide had advantages in terms of weight loss and glucose lowering, dulaglutide had advantages in terms of generalisability of its cardiovascular (CV) benefit data to include a type 2 diabetes CV primary prevention population (covered in detail later) and both had evidence of CV benefit in a type 2 diabetes CV secondary prevention population. The efficacy section of the dulaglutide vs semaglutide 'Barber's Box' (Slide 22) clearly acknowledged the glucose lowering and weight loss advantages for semaglutide, with most of that section shaded blue. The CV-related shading of the efficacy section of the 'Barber's Box' reflected the much broader applicability of the CV benefit seen in REWIND to include a type 2 diabetes CV primary prevention population. As mentioned above, all aspects of the analysis that led to the shading for each section of the 'Barber's Box' were detailed both in the slides and to the audience. It was clear that at least half of the efficacy box was shaded blue, with the purple shading intentionally graded to appear less prominent, making Novo Nordisk's assertion that 'The overall weight of such selective comparison would conclude a subjective favourability for dulaglutide (sic)' incomprehensible.

Lilly stated that Novo Nordisk referred to the fact that the original, withdrawn, slide deck failed to provide references to data or publications for aspects of the comparison of dulaglutide and liraglutide. As outlined in Lilly's responses, the company proposed several additions to that

section, all of which had been incorporated in subsequent versions of the 'Barber's Box' slide deck.

Lilly stated that it did not understand Novo Nordisk's assertions that the approach misled health professionals to draw conclusions that the data related to all patients with type 2 diabetes and that was not transparent that differing data sources had been used. As stated above, all aspects of the analysis that led to the shading for each section of the 'Barber's Box' were detailed to the audience, with all data sources appropriately referenced.

2 Undue emphasis on trial sub-populations to draw indirect comparisons between trials

Lilly stated that Novo Nordisk had introduced a substantial number of assertions here that were not made in the inter-company dialogue correspondence.

Lilly stated that it would nevertheless respond in detail, as Novo Nordisk's inaccurate interpretation of the CVOTs was at the heart of its complaint.

Background

- Cardiovascular (CV) disease was a major cause of morbidity and mortality in type 2 diabetes.
- In recent years, several glucose-lowering therapies for type 2 diabetes had shown reduction in risk of CV events (such as myocardial infarction or stroke) in CVOTs.
- It was important in evaluating reduction of risk of CV events to determine whether a therapy had evidence of primary prevention, secondary prevention, or both.
- In a CV context, the World Health Organization defined:
    - **Primary prevention** as reduction in the incidence of CV events (such as myocardial infarction or stroke) in 'people with risk factors who have not yet developed clinically manifest cardiovascular disease'.
    - **Secondary prevention** as reduction in the incidence of CV events in 'people with established coronary heart disease, cerebrovascular disease or peripheral vascular disease (collectively termed [established] cardiovascular disease)'.
- Clarity on whether a therapy had demonstrated evidence of primary prevention and/or secondary prevention was critical for prescribing healthcare professionals, as the prescribing decision for individual patients would be influenced by whether they were in a primary or secondary CV prevention population and would be informed by the data from the respective products' CVOTs.
- Several studies had demonstrated that the proportion of a typical type 2 diabetes population that had established CV disease (secondary prevention) was about a third or less (Einarson *et al* 2018 and Lautsch D *et al*).
- CVOTs usually differed in terms of study design and populations, so it was not appropriate to compare study outcomes (such as glucose lowering, weight loss, CV hazard ratios) between studies.
- What was appropriate, and of great clinical importance given the background outlined above, was to analyse CV risk sub-analyses from individual CVOTs to determine whether they showed evidence of primary prevention, secondary prevention, or both.

- Amongst the CVOTs for GLP-1 receptor agonists (GLP-1 RAs), only the dulaglutide CVOT (REWIND) had demonstrated evidence of primary prevention in addition to evidence of secondary prevention.

Interpretation of the CVOTs LEADER, SUSTAIN 6 and REWIND

LEADER (liraglutide) and SUSTAIN 6 (semaglutide) had been assessed by the European Medicines Agency (EMA), the Food and Drug Administration (FDA), and the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) consensus report authors, who were unanimous in their views that both studies demonstrated evidence of CV benefit in patients with established CV disease (secondary prevention), but not in patients with CV risk factors (primary prevention):

- The EMA assessment report for LEADER states, 'These data indicated that liraglutide can reduce 3-point MACE [major adverse cardiovascular events], and especially CV-death in T2DM patients with established CV disease", pointing out that 'For subjects >60 years with risk factors only, no positive effect on MACE could be detected'.
- The EMA assessment report for semaglutide stated, 'In CVOT (sic) a number of subjects were included with risk factors only. In these subjects, no effect on MACE was seen, but the numbers were too small to draw firm conclusions (10 events with semaglutide and 9 events with placebo)'.
- The same conclusions were drawn by the FDA, with the indications relating to reduction of CV risk in the liraglutide and semaglutide US labels stating that each was, 'indicated … to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and <u>established cardiovascular disease</u> (emphasis added)' (Victoza U.S. Label and Ozempic U.S. Label).
- The study findings had also been reported in arguably the highest source of authority in diabetes care, the joint ADA and EASD consensus report, which was updated in 2019. The updated report stated, 'Most other CVOTs with GLP-1 receptor agonists [other than the dulaglutide CVOT, REWIND] had included a minority of patients with risk factors only but <u>without evidence of benefit on MACE outcomes in the lower-risk subgroups</u> (emphasis added) (Buse JB, *et al*. 2019).
- What the ADA/EASD consensus report was concluding, like the EMA assessment reports and the FDA, was that neither liraglutide nor semaglutide demonstrated evidence of CV benefit in patients with CV risk factors (the primary prevention population) in LEADER and SUSTAIN 6. As the consensus report pointed out, the numbers of patients in the primary prevention subgroups in LEADER and SUSTAIN 6 were small, so the findings represented 'absence of evidence' of primary prevention benefit, rather than 'evidence of absence' of effect. In other words, it was unknown what the effects of those therapies would be in a primary prevention population.
- The ADA/EASD consensus report concluded, 'To date, the level of evidence to support the use of GLP-1 receptor agonists for primary prevention [ie people with risk factors who had not yet developed clinically manifest, or established, CV disease] was strongest for dulaglutide but <u>lacking for other GLP-1 receptor agonists</u> (emphasis added)'.

It was clear therefore that the CV benefit demonstrated in LEADER and SUSTAIN 6 could be generalised to type 2 diabetes patients with established CV disease (secondary prevention) for whom benefit was demonstrated, but not to type 2 diabetes patients with CV risk factors (primary prevention) for whom benefit was not demonstrated.

In contrast to LEADER and SUSTAIN 6, REWIND demonstrated evidence of CV benefit in both patients with established CV disease and those with CV risk factors (Gerstein HC *et al* 2019). REWIND had also been assessed by the key regulatory and clinical sources of authority mentioned earlier, who were unanimous in their views that CV benefit in REWIND, uniquely amongst the GLP-1 RAs, was demonstrated in both patients with established CV disease (secondary prevention) and those with CV risk factors (primary prevention):

- Section 5.1 of the Trulicity SPC contained a series of forest plots (Figure 2) showing, amongst others, the subgroup analysis conducted to determine whether there was consistent CV benefit in patients with established CV disease ('prior CVD') and those with CV risk factors only ('no prior CVD'), showing 'consistency of effect across subgroups for the primary endpoint.
    - The same conclusion was drawn by the FDA, with the indication relating to reduction of CV risk in the dulaglutide US label stating that it was, 'indicated … to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus who have <u>established cardiovascular disease or multiple cardiovascular risk factors</u> (emphasis added)' (Trulicity US Label).
    - As mentioned, the 2019 update to the joint ADA/EASD consensus report stated, 'To date, the level of evidence to support the use of GLP-1 receptor agonists for primary prevention [i.e. people with risk factors who have not yet developed clinically manifest, or established, CV disease] is <u>strongest for dulaglutide but lacking for other GLP-1 receptor agonists</u> (emphasis added)'.
    - In contrasting the primary CV prevention benefit seen in REWIND, but not LEADER or SUSTAIN 6, the ADA/EASD consensus report stated 'Whether the differences in outcomes in trial subgroups without established CVD *a*re related to study details or to the assigned therapy is uncertain'.
    - In other words, the differences seen in primary prevention benefit between the studies could be due either to differences in the study populations or differences between the pharmacological effects of the therapies.

Lilly stated that the Barber's Box slide deck included all the relevant data sets and sources of authority to support these conclusions.

Lilly stated that it would now address the assertions made by Novo Nordisk in its complaint.

Lilly noted that Novo Nordisk pointed out that dulaglutide did not achieve statistical significance in the sub-population of patients without CV disease in REWIND and referred to the statement in the ADA/EASD consensus report to that effect. This statement in isolation, whilst true, had no bearing on interpretation of REWIND, as detailed below. Novo Nordisk appeared to believe that in order for one to conclude that REWIND demonstrated evidence of benefit in patients without established CV disease (ie those with CV risk factors), statistical significance would need to have been demonstrated within that specific CV risk sub-group. This was a fundamental misunderstanding of how CVOTs and the CV risk subgroup analyses were interpreted. In the analysis of intervention studies, it was often important to investigate whether treatment effects varied among subgroups of patients defined by individual characteristics. This was generally best done by using tests for interaction. If the subgroups were sufficiently large to allow a valid interaction analysis to be performed and if the test for interaction was not statistically significant, it signified that there was a consistent effect seen among the subgroups being analysed. As an example, in REWIND, the p value for the sex subgroup interaction

analysis was 0.60, (signifying that there was consistent benefit seen between males and females. Statistical significance was not achieved within each subgroup of males or females, but that was irrelevant as the study was powered for the total population rather than for men or women individually. Given that the overall study was positive, that there were sufficient numbers of both men and women to support a valid interaction analysis, and that there was consistent benefit seen between men and women, one would conclude that both groups benefited ie dulaglutide demonstrated CV benefit in both men and women in REWIND. If one were to interpret these data as Novo Nordisk was suggesting, one would have to conclude that neither men nor women derived benefit in a study that demonstrated benefit in the overall population, raising the intriguing question of who exactly did benefit. The point of the forest plots in the REWIND section of the dulaglutide SPC showing 'consistency of effect across subgroups for the primary endpoint' was to make the point, *inter alia*, that there was consistent CV benefit in patients with established CV disease ('prior CVD') and those with CV risk factors ('no prior CVD'), ie both groups benefited. To be clear, Lilly had never claimed that statistical significance was seen in the sub-population of patients without CV disease in REWIND as detailed above, it was neither true nor relevant to interpretation of the CV risk subgroup analysis.

Lilly referred to Novo Nordisk's comment that the ADA/EASD consensus report stated, 'Most other CVOTs with GLP-1 receptor agonists [other than REWIND] have included a minority of patients with risk factors only but without evidence of benefit on MACE outcomes in the lower-risk subgroups. Whether the differences in outcomes in trial subgroups without established CVD are related to study details or to the assigned therapy is uncertain. It was Lilly, in fact, who drew Novo Nordisk's attention to this statement, in Lilly's response dated 31 March 2020, to point out that Novo Nordisk's assertion that the evidence of primary prevention benefit seen in REWIND but not LEADER or SUSTAIN 6 was due to differences in trial inclusion populations was merely one possible explanation and therefore speculative. Whilst the point of the statement, as detailed earlier, was to signify that the primary prevention benefit seen in REWIND but not LEADER or SUSTAIN 6 could be due either to differences in the study populations or differences between the pharmacological effects of the therapies, it also clearly supported Lilly's arguments that it was appropriate to analyse CV risk sub-analyses from individual CVOTs to determine whether they showed evidence of primary prevention, secondary prevention, or both, and that REWIND but not LEADER or SUSTAIN 6 showed evidence of primary prevention, with two possible explanations for this difference. The statement was included in the current version of the 'Barber's Box' slide deck.

Lilly stated that Novo Nordisk's comment that Figure 1 in the ADA/EASD consensus report recommended that a GLP-1 RA with a label indication of reducing CVD events should be considered but Novo Nordisk neglected to mention what the product labels specifically said in that regard. The differences in generalisability of the CV benefit data for dulaglutide, liraglutide and semaglutide were implicit in the EU labels. They all stated, in section 4.1, 'For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1'. Section 5.1 of the dulaglutide SPC, but not the liraglutide or semaglutide SPCs, contained a series of forest plots (Figure 2) showing 'consistency of effect across subgroups [including the primary and secondary prevention CV risk subgroups] for the primary endpoint'. The absence of these data from the liraglutide and semaglutide SPCs reflected the fact that neither of those therapies, as made explicit by the EMA assessment reports, FDA and ADA/EASD consensus report, had demonstrated CV benefit in a primary CV prevention population. The FDA labels were explicit, with the liraglutide and semaglutide US labels stating that each was, 'indicated … to reduce the risk of major adverse

cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease' (emphasis added) whilst the indication relating to reduction of CV risk in the dulaglutide US label stated that it was, 'indicated … to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus who had established cardiovascular disease or multiple cardiovascular risk factors' (emphasis added).

With regard to Novo Nordisk's comment about the 2019 European Society of Cardiology (ESC) Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD, Lilly submitted that it had reviewed page 298 and could find no mention of the recommendations Novo Nordisk referred to. Be it as it may, the ESC guidelines did not follow the World Health Organization's approach of categorization of CV risk into primary and secondary prevention, so unlike the EMA, FDA, and ADA/EASD consensus report, were silent on the subject of the CVOT CV risk sub-analyses. This was merely a different approach to CV risk in patients and in no way offered a different interpretation of the CVOTs than those made by the EMA, FDA, and ADA/EASD consensus report.

Lilly stated that it did not understand Novo Nordisk's point about needing to match statements from EMA reports for each therapy. Lilly had judiciously chosen relevant statements from appropriate sources of authority to inform the discussion and had included them at appropriate points in the presentation.

Lilly made a detailed submission about Novo Nordisk's mention of a separate inter-company dialogue in which it asserted Lilly, 'agreed that outcome data between the diabetes CVOTs should not be compared directly due to differences in trial designs and conduct'. Lilly stated that it had consistently agreed with Novo Nordisk that study outcomes should not be directly compared, but that was a completely different matter from reporting whether the individual studies showed evidence of primary prevention, secondary prevention, or both.

Lilly stated that Novo Nordisk also asserted that in the separate inter-company dialogue Lilly, 'agreed … that audiences should not be misled regarding the lack of statistical significance achieved in the REWIND cardiovascular sub-group populations'. Lilly stated that it disagreed entirely with Novo Nordisk's representation of Lilly's comments and made a detailed submission in this regard. What Lilly agreed to not do was present the claims in the circumstances that Novo Nordisk described, which was a combination of using the phrase 'unique and unprecedented'.

3 Cherry picking of data resulting in misleading and unbalanced presentation and conclusions

Lilly stated that Novo Nordisk had yet again introduced a substantial number of assertions here that were not made in their inter-company dialogue correspondence.

As outlined earlier, Lilly disagreed with Novo Nordisk's assertions that it had employed 'cherry picking'. Lilly had judiciously chosen relevant statements from appropriate sources of authority to inform the discussion, ensuring that Lilly maintained the balance imposed by the 'Barber's Box' framework. Novo Nordisk argued that Lilly should have included a statement from the ADA/EASD consensus report that, 'GLP-1 receptor agonists had high glucose-lowering efficacy, but with variation within the drug class. Evidence suggested that the effect might be greatest for semaglutide once weekly, followed by dulaglutide and liraglutide'. This would clearly be superfluous given that Lilly presented the glucose lowering data from SUSTAIN 7 and AWARD

6, making clear that injectable semaglutide had greater glucose lowering than dulaglutide and that dulaglutide and liraglutide had similar glucose lowering.

Lilly noted that Novo Nordisk had argued that the patient reported outcomes from SUSTAIN 7 and AWARD 6 should be included in the Barber's Box. As Lilly outlined in its letter dated 27 April 2020, the company proposed including the PREFER and Gelhorn studies, both of which were crossover studies allowing patients to compare the product devices and dosing requirements directly. Both these studies had been incorporated in versions of the 'Barber's Box' slide deck that followed the original, withdrawn, slide deck that Novo Nordisk challenged. Furthermore, as Lilly pointed out in intercompany dialogue patient reported outcomes from SUSTAIN 7 and AWARD 6 did not evaluate patient preference, as they were parallel-group (as opposed to crossover) studies that did not allow patients to directly compare any attributes of the therapies, including injection devices and dose-titration regimens, with each other.

Lilly stated that Novo Nordisk was now introducing new arguments that other aspects of product characteristics should be included in the analysis. Lilly did not agree that the well-known class effect of tachycardia was remotely like the warning language for semaglutide regarding the risk of diabetic retinopathy complications. Low grade tachycardia, whether common or less common, occurs with all the GLP-1 RAs as an adverse reaction, and all the GLP-1 RAs studied in CVOTs have been shown to be at least safe from a CV risk perspective and in some cases, such as REWIND, LEADER and SUSTAIN 6, to provide CV benefit, despite tachycardia. In contrast, complications of diabetic retinopathy were clearly very serious and potentially life changing. In terms of warning language in EU SPCs, this safety risk was unique to semaglutide within the GLP-1 RA class, with increased risk of diabetic retinopathy complications in patients treated with insulin and semaglutide, with its associated monitoring requirements, appearing in 'Section 4.4 Special Warnings and precautions for use' in the semaglutide SPC. None of the other five GLP-1 RAs marketed in the UK had this precautionary language in their SPCs. Novo Nordisk argued that the SUSTAIN 7 retinopathy data was relevant to the discussion, but as the semaglutide SPC stated, 'Systematic evaluation of diabetic retinopathy complications was only performed in the cardiovascular outcomes trial' (SUSTAIN 6), which was a 2-year clinical trial investigating 3,297 patients with type 2 diabetes. The slide on monitoring considerations for patients with diabetic retinopathy and treated with insulin was not intended to be a risk analysis of either therapy regarding diabetic retinopathy. Those risk analyses had already been conducted, as they should be, by the EMA. The slide simply reflected a requirement for semaglutide in its SPC that did not exist for dulaglutide, conveying a key difference in monitoring requirements between these two agents and therefore an advantage for dulaglutide in that specific context.

Lilly stated that it did not understand Novo Nordisk's point about the different number of pens required per month being relevant to patient considerations, as they had presented neither arguments nor data to support why one pen per month would be an advantage for patients compared with four pens.

In conclusion, slide deck PP-DG-GB-0573 was retired on 26 March 2020 and had not been used since, all the changes Lilly proposed in the company's responses dated 31 March 2020 and 27 April 2020 had been incorporated in subsequent versions of the 'Barber's Box' slide deck, and, for all the reasons detailed above, Lilly did not agree with Novo Nordisk's allegations of breaches of Clauses 7.2, 7.3, 7.4, 7.8, 7.9 and 9.1 of the Code.

PANEL RULING

The Panel noted that the presentation at issue was titled 'Barber's Box comparison of GLP-1 receptor agonists'. The Panel noted Lilly's explanation that the 'Barber's Box' framework was derived from the principles outlined in Nick Barber's 1995 BMJ publication with evolution of the framework over time as appropriate. In the publication, Barber proposed four aims (efficacy, safety and tolerability, cost and patient factors) which a prescriber should consider when prescribing and monitoring a medicine to be used as an aid for discussion and decision making. The Panel noted Lilly's submission that the approach was considered by health professionals – through consistent feedback in response to the presentations – to exemplify a fair and balanced approach, as it included all the key attributes that formulary committees and health professionals would consider in their decision making. The Panel further noted Lilly's submission that this approach ensured complete balance in comparison of therapies by highlighting all key attributes, including those where comparison with its product dulaglutide clearly favoured competitor products. The colouring of each component of the 'Barber's Box' was designed to reflect how the therapies compared when considering all relevant aspects of an attribute, which might include generalisability of study data or requirements for specific safety monitoring.

The Panel noted that slide deck PP-DG-GB-0573 was retired on 26 March 2020 and was the version of the presentation at issue. An independent referee decided that inter-company dialogue had been unsuccessful. The Panel noted that, in accordance with Paragraph 5.3 of the Constitution and Procedure, the decision of the independent referee in this regard was final. The Panel noted Lilly's submission that Novo Nordisk had introduced a substantial number of assertions at Points 1 and 2 that were not made in the inter-company dialogue. The Panel noted that Lilly did not provide specific details in this regard. The Panel noted the independent referee's decision that the case should be referred to the Panel for its consideration of all matters arising within it on their merits and the Panel proceeded on that basis.

1 Alleged selective comparison between products, resulting in misleading and unsubstantiated claims

The Panel noted Novo Nordisk's concern with the manner and degree to which Lilly had chosen to shade each box throughout the presentation and that the resulting strong conclusions and claims drawn between the products was subjective, and not substantiated by any peer review publication, health technology or regulatory assessment. Novo Nordisk alleged that it misled a health professional to draw a conclusion that the data related to all patients with type 2 diabetes and was not transparent that differing data sources and data sets within those sources had been used. In this regard, the Panel noted that Novo Nordisk specifically referred to Slide 22 and alleged that weight and glucose lowering efficacy conclusions from the direct head-to-head data of SUSTAIN 7 were combined with selective indirect comparisons between REWIND and SUSTAIN 6 sub-population cardiovascular data to conclude a subjective degree of shading; the overall weight of which would conclude a subjective favourability for dulaglutide.

The Panel noted Lilly's submission that the efficacy section of the dulaglutide vs semaglutide 'Barber's Box' on Slide 22 acknowledged the glucose lowering and weight loss advantages for semaglutide, with most of that section shaded blue making Novo Nordisk's assertion that 'The overall weight of such selective comparison would conclude a subjective favourability for dulaglutide (sic)' incomprehensible. The purple shading (favouring semaglutide) was intentionally graded to appear less prominent and reflected the much broader applicability of the CV benefit seen in REWIND to include a type 2 diabetes CV primary prevention population.

The Panel queried Lilly's claim for CV benefit in a type 2 diabetes CV primary prevention population noting that in the REWIND (Trulicity) trial, statistical significance was not met within each of the individual sub-groups including that which included patients that had risk of cardiovascular disease (primary prevention).

The Panel further noted Lilly's submission that all aspects of the analysis that led to the shading for each section of the 'Barber's Box' were detailed in the slides and hence to the audience; the colour shading was thus not seen in isolation but was always contextualised by the preceding analyses.

The Panel noted the slides preceding Slide 22 beginning at Slide 18 detailed advantages for dulaglutide in several clinical contexts. Slide 19 titled 'Efficacy: SUSTAIN 7' featured comparative bar charts comparing weight and glucose lowering data for semaglutide and dulaglutide from SUSTAIN-7. Slide 20 titled 'Efficacy: Cardiovascular Outcome trials' included adjacent visuals detailing study populations from REWIND and SUSTAIN-6. Slide 21 was also titled 'Efficacy: Cardiovascular Outcome trials' and included cardiovascular outcomes on adjacent forest plots, for REWIND (dulaglutide) and SUSTAIN-6 (semaglutide). The Panel queried the title of Slides 20 and 21 noting that REWIND and SUSTAIN-6 were cardiovascular safety trials and were not designed to demonstrate efficacy. The Panel did not know how the speaker introduced the Barber's Box framework, nor did it have a copy of the speaker notes. Nonetheless, the Panel noted that each slide should be capable of standing alone with regard to the requirements of the Code. Neither the slide at issue nor the preceding slides bore any explanation about the basis for the selection and comparison of the data. It was not clear from Slide 22 what differing data sources and data sets within those sources had been used to determine the shading.

Overall, the Panel considered that the presentation contained little information about the Barber's Box nor were relevant caveats presented in the slides to enable the audience to know how much weight to attach to the shaded Barber's Boxes including at Slides 22, 31 and 34. This was particularly important given the gradations of shading within the comparative efficacy boxes which the Panel considered audiences would necessarily, in the absence of any quantitative information and caveats on the slides, interpret differently. The Panel considered that the failure to provide sufficient information, such as relevant caveats on the shaded slides in question, meant that the presentation was misleading and the implications of the shaded comparative efficacy box were incapable of substantiation. A breach of Clauses 7.2, 7.3 and 7.4 was ruled.

The Panel noted that, contrary to Novo Nordisk's allegation, Slide 22 showed that efficacy favoured semaglutide. On this very narrow ground, the Panel did not consider that the shading of the efficacy section of the Barber's box on Slide 22 misleading implied a subjective favourability for dulaglutide as alleged and based on the narrow allegation, no breach of Clauses 7.2, 7.3, 7.4 and 7.8 were ruled.

The Panel noted that Slides 31 and 34 included the Barber's Box comparison of dulaglutide 1.5mg and liraglutide 1.8mg. The Efficacy and Safety/Tolerability box were referenced to Dungan *et al* 2014 and the Cost box to MIMS. The Panel therefore did not consider that Novo Nordisk had established that there was no reference to data or publications and therefore no substantiation at all for the shading of the boxes as alleged and based on the very narrow allegation no breach of Clause 7.4 was ruled.

2 Alleged undue emphasis on trial sub-populations to draw indirect comparisons between trials

The Panel noted that it appeared from Novo Nordisk's complaint that this allegation was in relation to Slide 21 which was titled 'Efficacy: Cardiovascular Outcome Trials'. The slide included a forest plot representing results of Events/patients (%) for dulaglutide vs placebo for patients with established CVD and no established CVD from the REWIND trial. Next to this was a similar forest plot representing results for semaglutide vs placebo from the SUSTAIN-6 trial. To the right of these forest plots it stated in a prominent highlighted box '**2019 Update to ADA/EASD Consensus Report** "...the level of evidence to support the use of GLP-1 receptor agonists for the primary prevention is strongest for dulaglutide but lacking for other GLP-1 receptor agonists"'.

The forest plot relating to REWIND showed favourability for dulaglutide vs placebo overall and in the subgroups of patients with and without established CVD. Below the forest plot it stated '**ADA Standards in Medical Care for Diabetes**...there was consistent benefit in the dulaglutide trial in patients with and without established ASCVD'.

The forest plot relating to SUSTAIN-6 showed favourability for semaglutide vs placebo overall and in the subgroup of patients with established CVD vs placebo but showed no difference in the subgroup without established cardiovascular disease. Below this forest plot it stated '**EMA Assessment Report**". In [the] CVOT a number of subjects were included with risk factors "only". In these subjects, no effect on MACE was seen, but the numbers were too small to draw firm conclusions"'.

The Panel noted Novo Nordisk's submission that the REWIND and SUSTAIN 6 trials were both designed and powered to demonstrate potential differences in Major Adverse Cardiovascular Events (MACE) as a composite primary endpoint for the full trial population (a blended at-risk population). Any subgroup sensitivity analyses were to demonstrate heterogeneity of the primary composite outcome. Neither product showed a statistically significant cardiovascular outcome benefit in the sub-population. The Panel further noted Novo Nordisk's submission that whilst the ADA/EASD consensus report mentioned that the level of evidence in the sub-population group without established cardiovascular disease was strongest for dulaglutide, it also stated that dulaglutide did not achieve statistical significance in this sub-population. Furthermore, the ADA/EASD Consensus report highlighted that the other GLP-1RA CVOTs included fewer participants in this sub-population and therefore it was currently unknown if the numerical benefit seen in REWIND was due to the therapy or differences between the GLP-1RA CVOT designs which was omitted from the presentation.

The Panel noted that Ozempic (semaglutide) and Trulicity (dulaglutide) were similarly indicated and bore in mind the differences and similarities between the SPCs for both medicines with respect to effects on glycaemic control and cardiovascular events. The Panel did not consider that the FDA licence indications of dulaglutide (Trulicity) and Ozempic (semaglutide) referred to by Lilly were relevant to this case. Further, the Panel noted that the overall guidance of the ADA/EASD consensus report was that any GLP-1RA with a label indication for reducing cardiovascular disease (CVD) events should be considered. The Panel further noted Novo Nordisk's submission that whilst not included in the presentation at issue, other relevant international guidelines such as 2019 European Society of Cardiology Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD equally recommended dulaglutide, liraglutide and semaglutide in patients with high/very high risk of

CVD and classified the level of evidence for all agents to be the same (page 298). The Panel noted Lilly's submission that it had reviewed page 298 and could find no mention of the recommendations Novo Nordisk referred to. The Panel noted that it could not find the information referred to by Novo Nordisk on page 298 of the document submitted by Novo Nordisk. However, a table on page 286 titled 'Recommendations for glucose-lowering treatment for patients with diabetes stated that "Liraglutide, semaglutide or dulaglutide are recommended in patients with T2DM and CVD, or at very high/high CV risk, to reduce CV events"'. All three medicines were listed as having Class 1 level of recommendation and A level of evidence.

The Panel considered that the presentation of the CVOT outcomes on Slide 21 and inclusion of the selected statements from the 2019 Update to the ADA/EASD Consensus Report and the ADA Standards in Medical Care for Diabetes and EMA Assessment Report, without reference to the lack of statistical significance achieved in the REWIND sub-group population without established CVD and the failure to highlight that it was currently unknown whether the numerical benefit seen in REWIND was due to the therapy or differences between the GLP-1RA CVOT designs, implied an advantage of dulaglutide over semaglutide which was misleading and incapable of substantiation and breaches of Clauses 7.2, 7.3, 7.8 and 7.4 were ruled.

The Panel noted that, similarly, Slide 33 included the forest plot in relation to the REWIND study and the same statement from the ADA Standards in Medical Care for Diabetes as described above. Next to it was a similar forest plot in relation to the LEADER study. Below this it stated '**EMA Assessment Report**". These data indicate that liraglutide can reduce 3-point MACE, and especially CV-death in T2DM patients with established CV disease". "For subjects >60 years with risk factors only, no positive effect on MACE could be detected"'.

The Panel noted that the forest plot with regard to liraglutide showed favourability for liraglutide overall and in the subgroup of patients with established CVD vs placebo but showed favourability for placebo in the subgroup without established cardiovascular disease.

Similar to Slide 21, to the right of these forest plots it stated '**2019 Update to ADA/EASD Consensus Report** "...the level of evidence to support the use of GLP-1 receptor agonists for the primary prevention is strongest for dulaglutide but lacking for other GLP-1 receptor agonists"'.

On the evidence before it, the Panel considered that the presentation of the trial outcomes on Slide 33 and inclusion of the statements from the 2019 Update to the ADA/EASD Consensus Report and the ADA Standards in Medical Care for Diabetes and EMA Assessment Report, without reference to the lack of statistical significance achieved in the REWIND sub-group population without established CVD and the failure to highlight that it was currently unknown if the numerical benefit seen in REWIND was due to the therapy or differences between the GLP-1RA CVOT designs, implied an advantage of dulaglutide over liraglutide which was misleading and incapable of substantiation and breaches of Clauses 7.2, 7.3, 7.8 and 7.4 were ruled.

3 Cherry picking of data resulting in misleading and unbalanced presentation and conclusions

The Panel noted that, in addition to Novo Nordisk's concern that only selected statements pertaining to the ADA/EASD consensus report had been included which was covered at Point 2, Novo Nordisk further alleged that there were other equally strong quotes from the original report in favour of semaglutide which were relevant and yet not presented. The example given was

'GLP-1 receptor agonists have high glucose-lowering efficacy, but with variation within the drug class. Evidence suggests that the effect may be greatest for semaglutide once weekly, followed by dulaglutide and liraglutide' (Davies *et al* 2018). The Panel noted Lilly's submission that including this statement would be superfluous given that Lilly presented the glucose lowering data from SUSTAIN 7 and AWARD 6, making it clear that injectable semaglutide had greater glucose lowering than dulaglutide and that dulaglutide and liraglutide had similar glucose lowering effect. The Panel noted that whilst AWARD-6 was not referred to within the presentation in question, Slide 19 was titled 'Efficacy: SUSTAIN 7' and included a graph from SUSTAIN 7 showing the change from baseline (%) of HbA1c for semaglutide 0.5mg and 1.0mg vs dulaglutide 0.75mg and 1.5mg respectively which showed that at low and high doses, semaglutide was superior to dulaglutide in improving glycaemic control. The Panel did not consider that Novo Nordisk had established that failing to refer to the quote 'GLP-1 receptor agonists have high glucose-lowering efficacy, but with variation within the drug class. Evidence suggests that the effect may be greatest for semaglutide once weekly, followed by dulaglutide and liraglutide' from the ADA/EASD Consensus Report was misleading as alleged and no breach of Clauses 7.2 and 7.3 were ruled.

The Panel noted Novo Nordisk's further allegation that Lilly had chosen to highlight one favourable difference between the semaglutide and dulaglutide SPCs, that of diabetic retinopathy yet there were many other relevant differences within the SPCs when evaluating which product to prescribe according to this framework. In this regard, the Panel noted Novo Nordisk's submission that another important safety consideration could be that the dulaglutide SPC highlighted atrioventricular block and sinus tachycardia as common whilst for semaglutide increased heart rate was listed as uncommon. In addition, for the patient considerations aspect of the framework, an important consideration could be that only one semaglutide pen was needed per month whilst four pens were required if using dulaglutide.

The Panel noted that Slide 24 was headed 'Safety/tolerability: Additional monitoring considerations for patients with diabetic retinopathy and treated with insulin'. It included a bar graph showing the share of GLP-1RA prescribing in combination with insulins stated that the prevalence of diabetic retinopathy in people with type 2 diabetes was in the order of 25.2% and included a grey box on the left-hand side of the slide which stated 'Semaglutide SmPC: Caution should be exercised when using semaglutide in patients with diabetic retinopathy treated with insulin. These patients should be monitored closely and treated according to clinical guidelines'. The Panel noted that Section 4.4 of the Ozempic (semaglutide) SPC stated beneath the heading 'Diabetic retinopathy', 'In patients with diabetic retinopathy treated with insulin and semaglutide, an increased risk of developing diabetic retinopathy complications has been observed (See section 4.8). Caution should be exercised when using semaglutide in patients with diabetic retinopathy treated with insulin. These patients should be monitored closely and treated according to clinical guidelines. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded'. The Panel noted Lilly's submission that none of the other five GLP-1 RAs marketed in the UK had this precautionary language in their SPCs.

The Panel noted that it appeared that the only head-to-head study between semaglutide and dulaglutide was SUSTAIN 7, a randomised, open-label, phase 3b trial comparing semaglutide versus dulaglutide once weekly in patients with type 2 diabetes, in which adverse events of diabetic retinopathy were reported by two patients (1%) receiving semaglutide 0·5mg, two patients (1%) receiving dulaglutide 0·75 mg, two patients (1%) receiving semaglutide 1·0 mg, and three patients (1%) receiving dulaglutide 1·5 mg.

The Panel noted Novo Nordisk's submission that throughout the course of inter-company dialogue, Lilly had refused to include the relevant, available, robust, phase 3a head-to-head data (SUSTAIN 7 and AWARD 6) pertaining to safety data and patient reported outcomes between the products being compared including the head-to-head retinopathy data from SUSTAIN 7. In this regard, the Panel noted that whilst AWARD-6 was not referred to within the presentation before it, Slide 23 was titled 'Safety/tolerability: SUSTAIN 7 adverse events (extract)'; diabetic retinopathy, however, was not referred to.

The Panel further noted Lilly's submission that patient reported outcomes from SUSTAIN 7 and AWARD 6 did not evaluate patient preference, as they were parallel-group (as opposed to crossover) studies that did not allow patients to directly compare any attributes of the therapies, including injection devices and dose-titration regimens, with each other.

The Panel further noted that Lilly disagreed that the well-known class effect of tachycardia was remotely like the warning language for semaglutide regarding the risk of diabetic retinopathy complications. Low grade tachycardia, whether common or less common, occurred with all the GLP-1 RAs as an adverse reaction, and all the GLP-1 RAs studied in CVOTs have been shown to be at least safe from a CV risk perspective and in some cases, such as REWIND, LEADER and SUSTAIN 6, to provide CV benefit, despite tachycardia. In contrast, complications of diabetic retinopathy were clearly very serious and potentially life changing. Novo Nordisk argued that the SUSTAIN 7 retinopathy data was relevant to the discussion, but as the semaglutide SPC stated, 'Systematic evaluation of diabetic retinopathy complications was only performed in the cardiovascular outcomes trial' (SUSTAIN 6), which was a 2-year clinical trial investigating 3,297 patients with type 2 diabetes. The Panel noted Novo Nordisk's submission that the slide on monitoring considerations for patients with diabetic retinopathy and treated with insulin was not intended to be a risk analysis of either therapy regarding diabetic retinopathy. Those risk analyses had already been conducted, as they should be, by the EMA. The slide simply reflected a requirement for semaglutide in its SPC that did not exist for dulaglutide, conveying a key difference in monitoring requirements between these two agents and therefore an advantage for dulaglutide in that specific context.

Lilly stated that it did not understand Novo Nordisk's point about the different number of pens required per month being relevant to patient considerations, as they had presented neither arguments nor data to support why one pen per month would be an advantage for patients compared with four pens.

Whilst in the Panel's view it was clear that the statement 'Caution should be exercised when using semaglutide in patients with diabetic retinopathy treated with insulin. These patients should be monitored closely and treated according to clinical guidelines' on Slide 24 was taken from the semaglutide SPC, the Panel noted that Slide 18 included 'Patients with diabetic retinopathy and treated with insulin' as an example of an advantage for dulaglutide in several clinical contexts.

Nonetheless, the Panel did not consider that inclusion of the statement from the semaglutide SPC with regard to diabetic retinopathy without referring to atrioventricular block and sinus tachycardia as being common for dulaglutide and increased heart rate as being uncommon for semaglutide was misleading as alleged or did not reflect the available evidence with regard to adverse reactions and, based on the complainant's narrow allegation, no breach of Clauses 7.2, 7.3 and 7.9 were ruled.

Nor did the Panel consider that Novo Nordisk had provided evidence to establish, on the balance of probabilities, that failure to mention that only one semaglutide pen was needed per month whilst four pens were required if using dulaglutide was an important factor for the patient considerations aspect of the framework was misleading as alleged. No breach of Clauses 7.2 and 7.3 were ruled.

With regard to Clause 9.1, the Panel noted Novo Nordisk's allegation that despite agreeing during a previous inter-company dialogue that indirect CVOT comparisons should not be made, Lilly continued to do so within this presentation. Additionally, the principle to use a subjective comparative framework to denote differentiation between products and make favourable claims was concerning and Novo Nordisk therefore concluded that this was a failure to maintain high standards.

In relation to the allegation that in principle to use a subjective comparative framework to denote differentiation between products and make favourable claims was concerning, the Panel did not consider that, in principle, it was necessarily unacceptable to use the Barber's Box framework so long as its presentation complied with the Code. The Panel therefore did not consider that Novo Nordisk had established that, in principle, using the Barber's Box framework in itself meant that Lilly had failed to maintain high standards and based on Novo Nordisk's narrow allegation on this point, no breach of Clause 9.1 was ruled.

The Panel noted the parties' submissions regarding inter-company dialogue and the presentation of CVOT data.

The Panel noted that in a letter from Lilly to Novo Nordisk dated 18 March 2020 in relation to a Trulicity video which appeared to be dated October 2019, Lilly agreed to make explicit that the study populations in the GLP-1 RA CVOTs were different and that the study outcomes should not be directly compared given the difference between the studies. No other inter-company dialogue that preceded the creation of the Barber's Box presentation at issue dated January 2020 was provided. The Panel noted Lilly's submission that it had consistently agreed with Novo Nordisk that study outcomes should not be directly compared, but that was a completely different matter from reporting whether the individual studies showed evidence of primary prevention, secondary prevention, or both. The Panel noted that slide deck PP-DG-GB-0573 was retired on 26 March 2020 and did not consider that Novo Nordisk had established, on the balance of probabilities, that despite agreeing during a previous inter-company dialogue that indirect CVOT comparisons should not be made, Lilly continued to do so within the Barber's Box presentation at issue. All of the inter-company dialogue post-dated the presentation at issue. No breach of Clause 9.1 was ruled in this regard.

Complaint received **19 August 2020**

Case completed **11 August 2022**