CASE AUTH/3245/9/19

ANONYMOUS GP (assisted by an Ex Employee*) v NOVO NORDISK

* This came to light during the appeal process

Promotion of Ozempic

An anonymous, contactable individual, who described him/herself as a GP was concerned about claims allegedly made by Novo Nordisk representatives with regard to Ozempic (semaglutide) and weight loss and cardiovascular benefits which he/she alleged was off-label promotion.

Ozempic was indicated for the treatment of certain adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise. It was a once weekly GLP-1 RA (glucagon-like peptide-1 receptor agonist).

The complainant was concerned that Novo Nordisk representatives were making superiority claims regarding the Sustain 6 trial when it was not powered for superiority.

The complainant stated that the reasons for Novo Nordisk promoting semaglutide for weight loss was obvious; many clinics were prescribing it for obese patients without diabetes as it was better than Saxenda but this was not what it was licensed for and the suicide rate was unknown.

The complainant further alleged that the representative was unable to substantiate the claims and give more information and also denigrated dapagliflozin, sitagliptin and canagliflozin.

The detailed response from Novo Nordisk is given below.

The Panel noted that the complainant had the burden of proving his/her complaint on the balance of probabilities. All complaints were judged on the evidence provided by the parties. The complainant had not provided the material at issue which meant that it was difficult for Novo Nordisk to respond. Novo Nordisk provided two leavepieces and an iDetailer for use with health professionals. It also provided a briefing document titled 'Ozempic Core Launch Guide'.

The Panel noted that Marso *et al* (the SUSTAIN 6 trial) evaluated cardiovascular outcomes in patients with type 2 diabetes on a standard-care regimen who were randomised to receive once-weekly subcutaneous semaglutide (0.5mg or 1mg) or volume-matched placebo. Patients had to have type 2 diabetes and HbA1c of 7% or above and either had not been treated with an antihyperglycaemic medicine or had been treated with no more than two oral antihyperglycaemic agents, with or without basal or pre-mixed insulin. Key inclusion criteria were an age of 50 or above with established CV disease, chronic heart failure or chronic kidney disease of stage 3 or higher or age 60 or above with at least one CV risk factor.

The primary composite outcome was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction (including silent) or nonfatal stroke. It was powered as a non-inferiority study. The non-inferiority margin was 1.8 for the upper boundary of the 95% confidence interval of the hazard ratio. Pre-specified secondary outcomes included the individual components of the primary composite outcome.

The hazard ratio for the composite primary outcome was 0.74; 95% confidence interval 0.58 to 0.95, p<0.001 for non-inferiority and p=0.02 for superiority. The authors stated that the study was not powered to show superiority, so such testing was not pre-specified or adjusted for multiplicity. However, the treatment effect of semaglutide and the accrual of more events than estimated resulted in a significantly lower risk of the primary outcome among patients in the semaglutide group. Patients were followed for a relatively short duration and were at high cardiovascular risk. The application of these findings to other populations and a longer duration of treatment was unknown. It was also unknown to what extent the greater glycated haemoglobin reductions in the semaglutide group contributed to the results. The authors concluded that in patients with type 2 diabetes at high cardiovascular risk, 'the rate of first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke was significantly lower in those receiving semaglutide than in those receiving placebo, which confirmed noninferiority'.

The Ozempic SPC stated that five trials (SUSTAIN 1–5) had the glycaemic efficacy assessment as the primary objective, while one trial (SUSTAIN 6) had cardiovascular outcome as the primary objective. The SPC stated that 'Treatment with semaglutide demonstrated sustained, statistically superior and clinically meaningful reductions in HbA_{1c} and body weight for up to 2 years compared to placebo and active control treatment (sitagliptin, insulin glargine, exenatide ER and dulaglutide)'. Information about the SUSTAIN trials in the Ozempic SPC included results for primary and secondary endpoints for SUSTAIN 6. The SPC included hazard ratios and confidence intervals but did not mention p values for SUSTAIN 6.

The first page of the 12 page Ozempic leavepiece included the claim 'Help adults with insufficiently controlled type 2 diabetes' above the main heading 'Realise the potential' followed by claims for superior glycaemic control and superior and sustained weight loss compared to dulaglutide, sitagliptin, exenatide once a week and insulin glargine. There was also a claim for 'CV benefits' versus placebo, both in addition to standard of care. The CV benefit claim included an asterisk to a footnote at the bottom of the page which stated, 'In SUSTAIN 6, Ozempic reduced major adverse CV risk (time to first occurrence of: CV death, non-fatal myocardial infarction, or non-fatal stroke) versus placebo in patients with type 2 diabetes at high CV risk treated with standard of care'. Page 2 referred to patients' struggle with poor glycaemic control and comorbidities referring to HbA1c, weight and CV disease. Page 3 of the leavepiece claimed that 'GLP RAs offer meaningful advantages over DPP-4 inhibitors'. This claim was followed by separate claims for Ozempic's superior glycaemic control and body weight reduction referring to significantly greater weight loss versus sitagliptin. A reference to CV benefits also appeared on the page stating that 'Ozempic offers CV risk reduction vs placebo, both in addition to standard of care [referenced to SUSTAIN 6] while DPP-4 inhibitors offer no CV risk reduction in their CVOTs [cardiovascular outcomes trials]'. This section was separated from the comparisons for superior glycaemic control and significantly greater weight loss by a vertical red line, however the information appeared

beneath the main heading to the page which referred to 'meaningful advantages' of GLP-1RAs over DPP-4 inhibitors. The next page gave more detail about the comparison between Ozempic and sitagliptin in HbA_{1C} and was followed by a page giving more detail about the weight loss comparison. The details of the SUSTAIN 6 study were set out on page 6 and the following page claimed that Ozempic significantly reduced the risk of CV events within a 2-year study. Within the graph titled 'Time to first confirmed major CV event (MACE)' it stated, in small light grey font, 'Hazard ratio: 0.74 (95% CI, 0.58-0.95) p<0.001 for non-inferiority'. This was the only reference in the leavepiece to SUSTAIN 6 being a non-inferiority study. Information was provided about the components of the primary composite endpoint including that there was no difference between Ozempic and placebo in relation to non-fatal myocardial infarction and CV death. There was a difference between Ozempic and placebo in relation to non-fatal stroke (p=0.04). The page claimed that when added to standard of care there was a 26% CV risk reduction vs placebo (ARR [absolute risk reduction] 2.3%).

The shorter leavepiece included similar claims. The Panel noted that the word 'superior' was not used to describe CV benefits in the leavepieces. The iDetailer had a number of sections including those labelled 'unmet need', 'superior efficacy' and 'CVOT'. The 'CVOT' section included details about SUSTAIN 6 and CV benefit. The claims were similar to that in the leavepieces. The iDetailer included the same graph as in the leavepieces and the reference to the hazard ratio and non-inferiority result. However, unlike the leavepieces the graph in the iDetailer also included 'p=0.02 for superiority post hoc'. This reflected the presentation of the data in the graph in the study other than the reference to 'post hoc'. The Ozempic Core Launch Guide briefing material did not mention that SUSTAIN 6 was powered as a non-inferiority study.

The Panel noted that, overall, the two leavepieces and the iDetailer made a number of superiority claims for Ozempic compared with other therapies. They each included the key messages referring to glycaemic control, weight loss and CV benefits.

The Panel noted that the Code 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 the SPC.

Section 5.1 of the Ozempic SPC stated that both improvement of glycaemic control and reduction of cardiovascular morbidity and mortality were an integral part of the treatment of type 2 diabetes.

The Panel considered that the complainant had not shown on the balance of probabilities that the claims regarding weight loss and CV outcomes were not presented in the context of the licensed indication for Ozempic ie the treatment of diabetes in certain patients. Information about SUSTAIN 6, CV outcomes and weight loss were included in the SPC. Bearing in mind the limited information provided by the complainant, the Panel considered that in the circumstances the complainant had not shown that Novo Nordisk had promoted Ozempic in a manner which was inconsistent with the particulars listed in its SPC. The Panel therefore ruled no breach of the Code in this regard. This ruling was unsuccessfully appealed by the complainant.

The Panel queried whether the material was sufficiently clear regarding the data for CV outcomes. The only reference to SUSTAIN 6 being a non-inferiority study was in small

light grey font included in a graph which appeared on one page of each of the leavepieces in a size similar to the text in the footnote. The iDetailer included similar information as the leavepieces but with the additional reference to 'p=0.02 for superiority post hoc'. The Panel considered the immediate and overall impression to a health professional. On balance, the Panel considered that the material was not sufficiently clear given the non-inferiority primary endpoint and further in relation to the iDetailer the SUSTAIN 6 authors caution as the study was not powered to show superiority. Nor was the material sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of Ozempic in terms of the claims for CV benefits. A breach of the Code was ruled. The Panel considered that Novo Nordisk had failed to maintain high standards in this regard and a breach of the Code was ruled.

The Panel noted that the complainant had not identified the Novo Nordisk representative who appeared to have discussed the product with him/her and left a leavepiece. The complainant had not clearly set out which claims were of concern to him/her as being incapable of substantiation or denigrated dapagliflozin, sitagliptin and canagliflozin and no details were provided about the alleged failure to respond to the complainant's request for more information. Nor was any detail provided by the complainant regarding his/her concerns about suicide risk. In the circumstances the complainant had not demonstrated, on the balance of probabilities, that there was a breach of the Code in this regard and the Panel therefore ruled no breach of the Code including Clause 2. The Panel's ruling of no breach of Clause 2 was unsuccessfully appealed by the complainant.

An anonymous, contactable individual, who described him/herself as a GP with a special interest (GPwSI) complained about claims allegedly made by Novo Nordisk representatives.

Ozempic (semaglutide) was indicated for the treatment of certain adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise. It was a once weekly GLP-1 RA (glucagon-like peptide-1 receptor agonist).

COMPLAINT

The complainant was concerned that Novo Nordisk representatives were making superiority claims regarding the Sustain 6 trial when it was not powered for superiority. The complainant stated that he/she tried to look for it in the leaflet left at his/her practice but could not find it. The complainant thought that it was not in the representatives iPad talking about weight loss, HbA1c and cardiovascular (CV) benefits.

It was not appropriate to call it CV benefits as the superiority was a *post hoc* finding and also semaglutide trials were powered for glycemic [sic]. Semaglutide was to treat diabetes not weight loss. Weight loss was a claim but weight outcome was a statement. The representative should be talking about weight loss claims [sic].

The complainant stated that it was very unprofessional and typical of pharmaceutical companies. The reasons for Novo Nordisk doing this was obvious as many clinics were prescribing semaglutide for obese patients without diabetes as it was better than Saxenda but this was not what it was licensed for and the suicide rate was unknown. The complainant was highly disappointed.

Further correspondence from the complainant stated that he/she spoke to another pharmaceutical company representative who told him/her to inform the PMCPA that this was clear off-label promotion especially in view of Novo Nordisk's obesity portfolio (both weight loss and CV) therefore it would constitute a Clause 2 breach.

Further the complainant could not share the leaflet that the representative had left as it had scribblings all over. In addition, as mentioned the only claim in the leaflet was for weight loss but the representatives' iPad went into weight loss as well as CV benefits/superiority. In contrast, the AstraZeneca representative did not talk about superiority.

The complainant stated that he/she did not really understand the nuances of the Code but tried his/her best to include the clauses that could possibly be infringed and cited 50 Clauses including Clauses 2, 3.2 and 9.1.

The complainant stated that the key clauses were Clauses 2, 3.2 and 9.1 given the concerns around the off-label promotion and misguiding because of the upcoming semaglutide obesity indication as well as riding on the success of LEADER (which was powered for superiority) CV data whilst Ozempic (or semaglutide diabetes) was not powered (primary endpoint) for CV superiority which had a wide confidence interval and low p value as well as it being a small, short trial and similarly none of the 10 efficacy trials being powered (primary endpoint) for weight therefore claiming weight loss was very clearly what Novo Nordisk did with Victoza back in 2010 (Clause 29) because it knew Saxenda was coming. The complainant recalled Novo Nordisk being reprimanded by the PMCPA given the uproar from doctors and medicines management.

The representative was unable to substantiate the claims and give more information and also denigrated dapagliflozin, sitagliptin and canagliflozin.

The complainant asked the PMCPA to consider the above and anything else deemed appropriate.

The case preparation manager informed the complainant that not all the clauses he/she cited were relevant including that some were statements of principle that were not capable of being breached and explained that the PMCPA would normally identify clauses when complaints came from outside the industry. The relevant clauses were agreed with the complainant. Therefore, Novo Nordisk was asked to bear in mind the provisions of Clauses 2, 3.2, 7.2, 7.4, 8.1, 9.1, 15.2 and 15.9 of the Code.

RESPONSE

Novo Nordisk stated it was surprised to learn that a representative of another pharmaceutical company had been commenting on its materials with a health professional. There had been no contact or initiation of intercompany dialogue as outlined in Paragraph 5.2 of the PMCPA Constitution and Procedure and as per the principles of self-regulation.

Ozempic was not indicated for the reduction of cardiovascular (CV) risk or weight loss in isolation and Novo Nordisk had not promoted it as such. The claims were made in the context of treatment of type 2 diabetes and the indication for Ozempic was:

> 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; and
- in addition to other medicinal products for the treatment of diabetes.

Since 2018, some diabetes treatments had had their indications changed from 'improvement of glycaemic control' to 'treatment of adults with insufficiently controlled type 2 diabetes mellitus …'. The Committee for Medicinal Products for Human Use (CHMP) recommended strengthening the wording to 'treatment of type 2 diabetes' as this was considered more relevant because the previous indication no longer adequately reflected the demonstrated effects of the diabetes treatment. The indication for such treatments encompassed both glycaemic control and results on clinical outcomes such as CV complications.

The European Medical Agency (EMA) considered both improvement of glycaemic control and reduction of cardiovascular morbidity and mortality an integral part of the treatment of type 2 diabetes, which could best be expressed in a single indication for Ozempic when it was licensed in February 2018. The additional wording in Section 5.1 of the SPC for Ozempic further explained the role of glycaemia and CV risk in type 2 diabetes therapy and was fully reflective of the EMA's view that a more holistic treatment approach was needed when treating patients with type 2 diabetes.

Section 5.1 of the Ozempic SPC stated:

> 'Both improvement of glycaemic control and reduction of cardiovascular morbidity and mortality are an integral part of the treatment of type 2 diabetes.'

Section 5.1 also highlighted the weight benefit seen with Ozempic:

> 'Treatment with semaglutide demonstrated sustained, statistically superior and clinically meaningful reductions in HbA1c and body weight for up to 2 years compared to placebo and active control treatment.'

Novo Nordisk submitted that claims relating to weight loss or cardiovascular benefits were never made in isolation and were always made in the context of treatment of type 2 diabetes and the indication for Ozempic. The indication was prominently and clearly placed upfront in all of the leavepieces and the iDetailer. Novo Nordisk addressed the complainant's specific concerns.

Superiority claims with regard to weight loss and Ozempic

Novo Nordisk was unclear about the statement made in the complainant's initial complaint letter that:

> 'The rep should be talking about weight loss claims ….'

Novo Nordisk response was based on its interpretation that the complainant meant to state that the Novo Nordisk representative should <u>not</u> be talking about weight loss claims.

The claim, 'superior and sustained weight loss compared to placebo and active control treatment (sitagliptin, insulin glargine, exenatide ER and dulaglutide)' was fully substantiated by the SPC (Section 5.1) and published studies by Pratley *et al* 2018, Ahrén 2017, Ahmann *et al*

2018 and Aroda *et al* 2017. Furthermore, all claims were specifically in the population for which Ozempic was indicated, ie adults with insufficiently controlled type 2 diabetes mellitus and not in isolation.

Novo Nordisk categorically refuted any allegation that it was in breach of Clauses 7.2, 7.4 or 3.2. The claim was accurate, fair, balanced, substantiable and was not inconsistent with the SPC.

Claims with regard to cardiovascular benefits and Ozempic

As stated above, any claims regarding cardiovascular (CV) benefit were made in the context of the treatment of type 2 diabetes and the indication for Ozempic.

In the two leavepieces provided, and the iDetailer used by representatives, the statements were in relation to a significant CV benefit (not superiority) compared with placebo in patients with type 2 diabetes at high CV risk treated with standard of care. This was supported by the SPC (Section 5.1) and also the SUSTAIN 6 study (Marso *et al* 2016).

SUSTAIN 6 cardiovascular outcomes trial

Novo Nordisk submitted that regulatory guidance specified the need to establish cardiovascular safety of new diabetes therapies in patients with type 2 diabetes in order to rule out excess cardiovascular risk.

The SUSTAIN 6 trial (Marso SP *et al* 2016) was one such Cardiovascular Outcome Trial (CVOT). It was a 104-week double-blind trial in which 3,297 patients with type 2 diabetes mellitus at high cardiovascular risk were randomised to either semaglutide 0.5mg once weekly, semaglutide 1mg once weekly or corresponding placebo in addition to standard-of-care. The primary endpoint was time from randomisation to first occurrence of a major adverse cardiovascular event (MACE): cardiovascular death, non-fatal myocardial infarction or non-fatal stroke for semaglutide compared to placebo.

The trial met its primary endpoint of non-inferiority and showed a significantly lower risk of major adverse cardiovascular events in patients receiving semaglutide vs placebo. A *post hoc* analysis was conducted and showed that the semaglutide arm achieved superior reductions in MACE as compared to the placebo. This finding was presented in the primary publication, published in the New England Journal of Medicine in 2016. With regard to the complainant's concerns about the size and length of the trial, this CVOT was deemed satisfactory by the regulators.

Conduct of representatives

Novo Nordisk submitted that the representatives had been fully briefed and trained about the indication of Ozempic and the SUSTAIN 6 trial. An implementation guide, which was used to brief the sales representatives about the selling strategy for Ozempic, and which also outlined the use of materials such as the iDetailer and leavepieces, was provided. Page 4 covered the overall strategy and clearly showed the intention to discuss superiority of reduction of HbA_{1c} first, then superiority of weight loss, then thirdly CV benefit (not superiority). All these were in line with the Ozempic indication. Page 17 focused on SUSTAIN 6 and CV benefits, and again, the claim was about benefits and not superiority. Novo Nordisk therefore categorically refuted any suggestion that it was in breach of Clause 15.9.

The representatives were trained not to make disparaging comments. Novo Nordisk refuted that a sales representative had made disparaging comments and not upheld high standards, and therefore refuted a breach of Clauses 8.1 and 15.2.

Leavepieces for use with GPs

Novo Nordisk would be happy to address the complainant's specific concerns regarding the leavepiece in question. It noted that the complainant followed up in further correspondence to the PMCPA (25 September 2019), stating:

> 'Unfortunately, I cannot share the leaflet that the rep had left with us as it had scribblings all over.'

This was obviously very disappointing to Novo Nordisk as it would assist in ensuring any concerns were addressed with specificity. Novo Nordisk queried if the complainant could perhaps redact the handwritten comments and provide a copy, or simply provide the job bag code of the leavepiece in question if it was not possible to provide the material itself?

Novo Nordisk submitted that it had not produced a leavepiece which had claims solely relating to weight loss, as referred to in the letter dated 25 September, and so it was unclear as to which material the complainant referred. Nor had Novo Nordisk produced a leavepiece which covered SUSTAIN 6 alone.

In the absence of information about the specific leavepiece, as requested, Novo Nordisk provided leavepieces which were used specifically with GPs (UK19OZM00122 and UKOZM00181) and in addition, the iDetailer used by the sales representatives. The points regarding claims of weight loss and CV benefits had been addressed above.

With regard to the additional comments made by the complainant, the allegations about off-label promotion with regard to weight loss had been addressed above. Novo Nordisk submitted that all claims were supported by trial data and were substantiated, therefore categorically refuted the allegation of a breach of Clause 7.4.

Novo Nordisk was unclear about the comment regarding suicide rates. There was no increased risk of suicide in patients treated with Ozempic, and it was not reported in Section 4.8 of the SPC.

In summary, Novo Nordisk submitted that the claims with regard to weight loss and CV benefit were made in the context of treatment of type 2 diabetes, were not misleading and were fully supported by published trial data. The representatives were fully trained and briefed and had not disparaged other companies' products or failed to maintain high standards. There had been no off-label promotion, and therefore Novo Nordisk strongly refuted that it was in breach of Clauses 15.9, 15.2, 9.1, 8.1, 7.4, 7.2, 3.2 or Clause 2.

PANEL RULING

The Panel noted that the complainant had the burden of proving his/her complaint on the balance of probabilities. All complaints were judged on the evidence provided by the parties. The complainant had not provided the material at issue which meant that it was difficult for Novo

Nordisk to respond. It appeared that there might be some errors in the complaint. Novo Nordisk provided two leavepieces and an iDetailer aid for use with health professionals. It also provided a briefing document 'Ozempic Core Launch Guide'.

The Panel noted that Marso *et al* (the SUSTAIN 6 trial) evaluated cardiovascular outcomes in patients with type 2 diabetes on a standard-care regimen who were randomised to receive once-weekly subcutaneous semaglutide (0.5mg or 1mg) or volume-matched placebo for 104 weeks. Patients in the study had to have type 2 diabetes and HbA1c of 7% or above and either had not been treated with an antihyperglycaemic medicine or had been treated with no more than two oral antihyperglycaemic agents, with or without basal or pre-mixed insulin. Key inclusion criteria were an age of 50 or above with established CV disease, chronic heart failure or chronic kidney disease of stage 3 or higher or age 60 or above with at least one CV risk factor.

The primary composite outcome was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction (including silent) or nonfatal stroke. It was powered as a non-inferiority study. The non-inferiority margin was 1.8 for the upper boundary of the 95% confidence interval of the hazard ratio. Pre-specified secondary outcomes included the individual components of the primary composite outcome.

The hazard ratio for the composite primary outcome was 0.74; 95% confidence interval 0.58 to 0.95, $p<0.001$ for non-inferiority and $p=0.02$ for superiority. The authors stated that the study was not powered to show superiority, so such testing was not pre-specified or adjusted for multiplicity. However, the treatment effect of semaglutide and the accrual of more events than estimated resulted in a significantly lower risk of the primary outcome among patients in the semaglutide group. Patients were followed for a relatively short duration (2.1 years) and were at high cardiovascular risk. The generalisability of these findings to other populations and a longer duration of treatment was unknown. It was also unknown to what extent the greater glycated haemoglobin reductions in the semaglutide group contributed to the results. The authors concluded that in patients with type 2 diabetes at high cardiovascular risk, 'the rate of first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke was significantly lower in those receiving semaglutide than in those receiving placebo, which confirmed **noninferiority**' (emphasis added).

The Ozempic SPC stated that five trials (SUSTAIN 1–5) had the glycaemic efficacy assessment as the primary objective, while one trial (SUSTAIN 6) had cardiovascular outcome as the primary objective. The SPC stated that 'Treatment with semaglutide demonstrated sustained, statistically superior and clinically meaningful reductions in HbA_{1c} and body weight for up to 2 years compared to placebo and active control treatment (sitagliptin, insulin glargine, exenatide ER and dulaglutide)'. Information about the SUSTAIN trials given in the Ozempic SPC included results for primary and secondary endpoints for SUSTAIN 6. The SPC included hazard ratios and confidence intervals but did not mention p values for SUSTAIN 6.

The first page of the 12 page Ozempic leavepiece (ref UK19OZM00122) included the claim 'Help adults with insufficiently controlled type 2 diabetes' above the main heading 'Realise the potential' followed by claims for superior glycaemic control and superior and sustained weight loss compared to dulaglutide, sitagliptin, exenatide once a week and insulin glargine. There was also a claim for 'CV benefits' versus placebo, both in addition to standard of care. The CV benefit claim included an asterisk to a footnote at the bottom of the page which stated, 'In SUSTAIN 6, Ozempic reduced major adverse CV risk (time to first occurrence of: CV death,

non-fatal myocardial infarction, or non-fatal stroke) versus placebo in patients with type 2 diabetes at high CV risk treated with standard of care'. Page 2 referred to patients' struggle with poor glycaemic control and comorbidities referring to HbA1c, weight and CV disease. Page 3 of the leavepiece claimed that 'GLP RAs offer meaningful advantages over DPP-4 inhibitors'. This claim was followed by separate claims for Ozempic's superior glycaemic control and body weight reduction referring to significantly greater weight loss versus sitagliptin. A reference to CV benefits also appeared on the page stating that 'Ozempic offers CV risk reduction vs placebo, both in addition to standard of care [referenced to SUSTAIN 6] while DPP-4 inhibitors offer no CV risk reduction in their CVOTs [cardiovascular outcomes trials]'. This section was separated from the comparisons for superior glycaemic control and significantly greater weight loss by a vertical red line, however the information appeared beneath the main heading to the page which referred to 'meaningful advantages' of GLP-1RAs over DPP-4 inhibitors. The next page gave more detail about the comparison between Ozempic and sitagliptin in HbA_{1C} and was followed by a page giving more detail about the weight loss comparison. The details of the SUSTAIN 6 study were set out on page 6 and the following page claimed that Ozempic significantly reduced the risk of CV events within a 2-year study. Within the graph titled 'Time to first confirmed major CV event (MACE)' it stated, in small light grey font, 'Hazard ratio: 0.74 (95% CI, 0.58-0.95) $p<0.001$ for non-inferiority'. This was the only reference in the leavepiece to SUSTAIN 6 being a non-inferiority study. Information was provided about the components of the primary composite endpoint including that there was no difference between Ozempic and placebo in relation to non-fatal myocardial infarction and CV death. There was a difference between Ozempic and placebo in relation to non-fatal stroke ($p=0.04$). The page claimed that when added to standard of care there was a 26% CV risk reduction vs placebo (ARR [absolute risk reduction] 2.3%).

The shorter leavepiece (ref UK19OZM00181) included similar claims. The Panel noted that the word 'superior' was not used to describe CV benefits in the leavepieces. The iDetailer (re UKOZS03180001) had a number of sections including those labelled 'unmet need', 'superior efficacy' and 'CVOT'. The 'CVOT' section included details about SUSTAIN 6 and CV benefit. The claims were similar to that in the leavepieces. The iDetailer included the same graph as in the leavepieces and the reference to the hazard ratio and non-inferiority result. However, unlike the leavepieces the graph in the iDetailer also included 'p=0.02 for superiority post hoc'. This reflected the presentation of the data in the graph in the study other than the reference to 'post hoc'. The Ozempic Core Launch Guide briefing material did not mention that SUSTAIN 6 was powered as a non-inferiority study.

The Panel noted that, overall, the two leavepieces and the iDetailer made a number of superiority claims for Ozempic compared with other therapies. They each included the key messages referring to glycaemic control, weight loss and CV benefits.

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 the SPC.

Section 5.1 of the Ozempic SPC stated that both improvement of glycaemic control and reduction of cardiovascular morbidity and mortality were an integral part of the treatment of type 2 diabetes.

The Panel considered that the complainant had not shown on the balance of probabilities that the claims regarding weight loss and CV outcomes were not presented in the context of the

licensed indication for Ozempic ie the treatment of diabetes in certain patients. Information about SUSTAIN 6, CV outcomes and weight loss were included in the SPC. Bearing in mind the limited information provided by the complainant the Panel considered that in the circumstances the complainant had not shown that Novo Nordisk had promoted Ozempic in a manner which was inconsistent with the particulars listed in its SPC. The Panel therefore ruled no breach of Clause 3.2 in this regard. This ruling was appealed by the complainant.

The Panel queried whether the material was sufficiently clear regarding the data for CV outcomes. The only reference to SUSTAIN 6 being a non-inferiority study was in small light grey font included in a graph which appeared on one page of each of the leavepieces in a size similar to the text in the footnote. The iDetailer included similar information as the leavepieces but with the additional reference to 'p=0.02 for superiority post hoc'. The Panel considered the immediate and overall impression to a health professional. On balance, the Panel considered that the material was not sufficiently clear given the non-inferiority primary endpoint and further in relation to the iDetailer the SUSTAIN 6 authors caution as the study was not powered to show superiority. Nor was the material sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of Ozempic in terms of the claims for CV benefits. A breach of Clause 7.2 was ruled. The Panel considered that Novo Nordisk had failed to maintain high standards in this regard and a breach of Clause 9.1 was ruled.

The Panel noted that the complainant had not identified the Novo Nordisk representative who appeared to have discussed the product with him/her and left a leavepiece. The complainant had not clearly set out which claims were of concern to him/her as being incapable of substantiation or denigrated dapagliflozin, sitagliptin and canagliflozin and no details were provided about the alleged failure to respond to the complainant's request for more information. Nor was any detail provided by the complainant regarding his/her concerns about suicide risk. In the circumstances the complainant had not demonstrated, on the balance of probabilities, that there was a breach of the Code in this regard and the Panel therefore ruled no breach of Clauses 7.2, 7.3, 7.4, 7.10, 8.1, 15.2, 15.9, 9.1 and 2. The Panel's ruling of no breach of Clause 2 was appealed by the complainant.

The Panel noted that the complainant provided a long list of clauses but had made no specific allegations in relation to many of these. The case preparation manager had not asked Novo Nordisk to comment on these clauses. The case preparation manager had not referred them to the Panel.

APPEAL BY THE COMPLAINANT

The complainant stated that he/she appealed the Panel's rulings of no breach of Clauses 3.2 and 2, and any others that the PMCPA thought were relevant, with regard to the weight loss claim. [The PMCPA advised the complainant it was for him/her to decide which clauses to appeal.]

The complainant alleged that there was a clear difference between the licensed indications for Saxenda and Victoza. Saxenda (liraglutide) was indicated for weight loss therefore weight loss claims were appropriate. Victoza (liraglutide) on the other hand was indicated for diabetes ie glucose management and could not have weight loss claims. Ozempic was indicated for diabetes management ie glycaemia not weight loss. Semaglutide higher dose (2.4mg) was currently undergoing clinical trials (STEP program) to seek an obesity indication however, Novo Nordisk was trying to promote off label now via Ozempic so that it could build its heritage brand

to help when semaglutide 2.4 launched. This was heavily frowned upon in the medical community and stopping these behaviours was what the PMCPA stood for.

The complainant alleged that Ozempic could only make a claim for glycemic reduction in line with Section 4.1 of SPC and not weight loss as there were specific products with trials powered via their primary endpoints (such as Belvique, Qsymia, Saxenda via their dedicated trials eg SCALE). There was a difference in power and design of SCALE trials as well as patient population ie obese and non-diabetic, and that was what led to the licensed indication for Saxenda warranting the right to promote weight loss.

The complainant alleged that clearly this was not what the SUSTAIN trials were powered for, not one of them. They were all powered for HbA1c primary endpoint, and the patient population had a way lower mean weight. This was why Ozempic was licensed for diabetes (glycemia) treatment and did not have the same Section 4.1 wording as Saxenda regarding weight management.

The complainant alleged that Novo Nordisk promoted Ozempic off label with regard to weight loss. As alluded to earlier, the PMCPA reprimanded (Clause 2) Novo Nordisk ten years ago for weight loss promotion for the exact same reasons and it was doing the same thing again. It was unacceptable – in terms of both patient safety and cost to the NHS. This made the medical community and the general public lose faith in the pharmaceutical industry. The complainant appreciated that not all pharmaceutical companies were the same, but Novo Nordisk had brought discredit to the entire industry.

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The complainant subsequently advised that he/she was assisted by an ex-employee. Novo Nordisk was so advised.

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COMMENTS FROM NOVO NORDISK

Novo Nordisk submitted that as stated in its response to the complaint, Ozempic was not indicated for weight loss and Novo Nordisk had not promoted it as such. Novo Nordisk had not produced a leavepiece which had claims solely relating to weight loss, as referred to by the complainant. Claims relating to weight loss for Ozempic were never made in isolation, always followed a glycaemic claim and were always made in the context of treatment of type 2 diabetes and the indication for Ozempic. The indication for Ozempic was prominently and clearly placed upfront in all of the leavepieces and the iDetailer. Therefore, Novo Nordisk categorically refuted the allegation regarding off-label promotion of Ozempic for weight loss.

Novo Nordisk submitted that the consideration of weight was an integral part in the management of patients with type 2 diabetes. The American Diabetes Association and European Association for the Study of Diabetes (ADA/EASD) consensus guideline of 2018 gave new recommendations for the management of hyperglycaemia in patients with type 2 diabetes. The guidelines stated that there were multiple factors which affected the choice of glucose-lowering medications and ‘the compelling need to minimise weight gain or promote weight loss was highlighted as a key consideration (copy provided).

Novo Nordisk submitted, therefore, that the effect of glucose-lowering medications on weight must be considered by health professionals. In addition, the latest NICE guideline for the management of type 2 diabetes in adults specifically had weight as a parameter for whether GLP-1 RA therapy should be continued:

> '1.6.29 Only continue GLP-1 mimetic therapy if the person with type 2 diabetes had had a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months).'

Novo Nordisk provided a copy of the guideline.

In relation to the complainant's reference to Novo Nordisk products licensed for weight loss (Saxenda) and those in development, Novo Nordisk strongly refuted the allegation that it was trying to use one portfolio to leverage the other. The UK obesity and diabetes portfolios were managed by separate business units with separate departments including sales teams, marketing teams and separate promotional materials. The complaint was about the promotion of Ozempic and Novo Nordisk's response focussed on Ozempic and made no reference to other Novo Nordisk products.

Novo Nordisk submitted that the claim for Ozempic of 'superior and sustained weight loss compared to placebo and active control treatment (sitagliptin, insulin glargine, exenatide ER and dulaglutide)' was fully substantiated by the SPC (Section 5.1) and published studies by Pratley *et al* 2018, Ahrén 2017, Ahmann *et al* 2018 and Aroda *et al* 2017. Furthermore, all claims were specifically in the population for which Ozempic was indicated, ie adults with insufficiently controlled type 2 diabetes mellitus and not in isolation. This claim was made in the context of treatment of type 2 diabetes. As outlined in the most recent guidelines, weight was an important factor to consider when choosing a glucose-lowering medication. There had been no off-label promotion, and therefore Novo Nordisk categorically refuted that it had breached Clause 3.2 and Clause 2.

Novo Nordisk submitted that it had significant concerns regarding the source of the complaint, and therefore the provision of the iDetailer in its entirety to the complainant. Novo Nordisk was concerned that there appeared to have been discussions/collusion by the complainant with a representative of another competing pharmaceutical company. Novo Nordisk also noted that the complainant refused to provide the copy of the material to which it referred, nor the job bag reference. This obviously made it more difficult for Novo Nordisk to address any concerns.

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It was confirmed with Novo Nordisk that the pages of the iDetailer that referred to weight could be shared with the complainant. The complainant was given the opportunity to provide further comments for his/her appeal in that regard.

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FINAL COMMENTS FROM THE COMPLAINANT AND FURTHER APPEAL COMMENT

The complainant alleged that Novo Nordisk had provided a contradicting response. Novo Nordisk stated that Ozempic was not indicated for weight loss and it had not been promoted as such; however, the pages from the iDetailer showed a clear message and promotion of weight

loss. The iDetailer clearly stated Ozempic was being promoted for obesity and for overweight patients which was outwith the licensed indication. This was the first time this material had been shared and it was heavily concerning that this was disparaging metformin – another off label promotion as metformin was not indicated for CV reduction; metformin was clearly indicated for weight loss in the type 2 diabetes space and in the paediatric population as follows:

> 'Treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone did not result in adequate glycaemic control.
> - In adults, metformin 850mg tablets might be used as monotherapy or in combination with other oral anti-diabetic agents, or with insulin.
> - In children from 10 years of age and adolescents, metformin tablets might be used as monotherapy or in combination with insulin.
>
> A reduction of diabetic complications had been shown in overweight type 2 diabetic patients treated with metformin as first-line therapy after diet failure (see 5.1 pharmacodynamic properties.)'

The complainant alleged that Ozempic was not indicated for weight loss or use in children; however, Novo Nordisk clearly demonstrated promotion of weight loss by drawing attention to obesity claims when (the header stated) metformin was not enough. The licences for metformin and Ozempic were utterly different as outlined above therefore Novo Nordisk had denigrated and promoted off label use of not only metformin but also its own product, Ozempic by falsely comparing it to metformin which had a clear weight loss licence in the type 2 diabetes space.

Further, the complainant alleged that Novo Nordisk had provided training and briefing to representatives (Novo Nordisk should be asked to share the briefing and training materials) that specifically called out weight as the very reason to prescribe especially against Trulicity, the number 1 selling weekly GLP-1. This was a clear and outright promotion of weight loss for which Ozempic was not indicated. Precisely what Novo Nordisk was reprimanded for in 2010, Clauses 2 and 3.2 amidst a myriad of other clauses.

The complainant noted that Novo Nordisk claimed in its response that the indication of Ozempic was stated prominently and clearly upfront in all its leavepieces and iDetailer but this was not true even in the materials in question. Section 4.1 of the SPC clearly referred to glycemic control and cardiovascular events ('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.), which was not stated in any of Novo Nordisk's materials. Section 4.1 of the SPC clearly did NOT talk about weight, only glycemia and CV events as mentioned above; therefore in the complainant's view Novo Nordisk had the clear intention to promote off label and mislead health professionals with regard to weight loss promotion.

The complainant confirmed that his/her complaint was still only regarding Ozempic being promoted off label for weight loss indication and not any other products. The other products quoted were to highlight Novo Nordisk's strategy to promote weight loss against Trulicity and also to contrast the label against metformin which was being denigrated and disguised off label promotion by Novo Nordisk as well as Novo Nordisk's obesity medication which had a different licence; Saxenda. Therefore, the complainant highlighted yet another attempt to fool the PMCPA Panel. The complainant stated that the majority of materials being used and certainly the pages from the iDetailer were drawn up and approved when obesity was part of the diabetes business unit in 2018/2019. The obesity medical function was still part of the diabetes business

unit, unlike the haemophilia business unit; this was intentional to influence the minds of signatories and approve semaglutide for promotion of weight loss in diabetes patients when it was not licensed for it. Even when they were separate business units (2020), the personnel moved fluidly between diabetes and obesity anyway, especially signatories and a number of staff who led obesity, had famously used the term Diabesity when talking to representatives. During 2018/2019, as number of signatories worked across diabetes and obesity, or diabesity. (The complainant used the initials of a number of Novo Nordisk staff in these regards). Also in 2019 a full time UK sales representative worked part time in obesity and part time in diabetes marketing, again deliberately to ensure the strategy to promote weight loss and evergreening semaglutide thereby ensuring that the strategy and messaging to lay the land for semaglutide obesity by promoting weight loss in Ozempic and aligning it with Saxenda's indication.

The complainant alleged that it was unclear why a manuscript of guidelines had been provided rather than the guidelines. Why had international guidelines been quoted when they were not the 'go to' by GPs and nurses? Moreover, the ADA/EASD was a consensus report and not a guideline and was deliberately misrepresented by Novo Nordisk in order to trick the PMCPA Panel just like it did health professionals. The NICE guideline was the most relevant in UK; and was the go-to reference used by health professionals especially GPs. It was clear that weight was not mentioned in these guidelines because NICE recognised that obesity was a separate condition and was currently scoping a separate obesity guideline. NICE was a cost-effectiveness guideline therefore the weight stopping rule was imposed due to the high costs of GLP-1 as there was a high proportion of discontinuation of GLP-1 mimetics given that the real-world results were not as inflated as in randomised clinical trials. Contrary to Novo Nordisk quoting NICE guidelines GLP-1 stopping rule 'Only continue GLP-1 mimetic therapy if the person had had a beneficial metabolic response (a reduction of at least 1.0 percentage point in HbA1c and a weight loss of at least 3% of initial body weight at 6 months)', Novo Nordisk had failed to quote this in all its materials, as could be seen in both the leavepiece and pages from the iDetailer. This was cherry-picking and misleading as it twisted part of NICE's advice indirectly in Ozempic's favour but not the stopping indication as per NICE guidelines used in Novo Nordisk's defence. Weight was an important consideration in the treatment of type 2 diabetes but it was wrong for Novo Nordisk to solely use this angle when the strategy in 2019 had been to gain all new business where Trulicity was being prescribed and the representatives had been trained and briefed to promote weight loss as the primary reason to prescribe Ozempic, that too straight after metformin when the metformin label clearly had substance for weight loss in type 2 diabetes and the other points denigrating metformin, as laid out above. This was yet another clear indication that Novo Nordisk's intention was to deliberately mislead GPs and promote the off-licence indication of weight management (compared to the metformin SPC and Saxenda SPC, which was what Novo Nordisk was preparing the market for with the semaglutide obesity launch).

The complainant stated his/her concerns were about the whole claim and behaviour of Novo Nordisk and in particular Clauses 2 and 3.2.

COMMENTS FROM NOVO NORDISK ON COMPLAINANT'S FURTHER APPEAL COMMENTS

Novo Nordisk submitted that as stated in its previous responses, it categorically refuted the allegation regarding the promotion of Ozempic for weight loss, and therefore denied a breach of Clause 3.2. The pages of the iDetailer provided to the complainant were a selection of pages; they did not provide the full context of Ozempic promotion. The indication was clear on the

iDetailer, as it was on the two leavepieces provided. The complainant initially raised concerns about a leavepiece and alleged that representatives had made claims about weight, however he/she refused to provide the leavepiece or identifying job bag number. Novo Nordisk took any complaint very seriously and co-operated fully whilst having no information regarding the exact leavepiece in question, nor dates of the alleged conversations with representatives. Novo Nordisk reiterated the point made in its previous responses that there were no leavepieces for Ozempic which focussed on weight alone, as alleged by the complainant. Any claims relating to weight were always in the context of the treatment of type 2 diabetes. Novo Nordisk fully supported the PMCPA ruling of no breach of Clauses 3.2 and 2.

With regard to Novo Nordisk staff working across different therapy areas the company submitted that this was standard practice in pharmaceutical companies to manage workload and staffing capacity. It was also common practice for staff to undertake a secondment into another role for career development.

Novo Nordisk was unclear regarding the comments relating to metformin. As the complainant had stated the complaint was about the promotion of Ozempic.

Novo Nordisk submitted that as the complainant had stated, UK health professionals would be familiar with the NICE guideline NG28, particularly those health professionals with whom the representatives were discussing treatment for their patients with type 2 diabetes. These health professionals would be aware of the GLP-1 RA 'target' or stopping rule, that included glycaemic as well as weight loss targets, and the recommendation that therapy should be stopped if these targets were not achieved. The NICE guidelines included information about weight management throughout therefore weight was an important consideration in the treatment of type 2 diabetes.

Novo Nordisk submitted that the American Diabetes Association and European Association for the study of Diabetes consensus report in 2018 was relevant to UK based healthcare professionals, and in addition one of the two primary authors was a UK endocrinologist working in the UK. The report was peer reviewed by a number of health professionals based in the UK, as listed in the acknowledgements section of the publication.

Novo Nordisk noted the confirmation that the complainant was being assisted by an ex-employee of Novo Nordisk. Novo Nordisk submitted that this was clear from the complainant's response which gave many details which would only have been known to someone in the course of their work at Novo Nordisk, such as email initials of many Novo Nordisk employees.

Novo Nordisk was concerned about the lack of transparency of the complainant with the PMCPA as initially he/she misleadingly stated that he/she did not have an interest to declare.

FINAL COMMENTS FROM THE COMPLAINANT

The complainant stated that it was disappointing that Novo Nordisk would take a below the belt shot when it did not even know the truth. This was classical of its deceitful behaviour. The complainant maintained that its declarations made to PMCPA were correct. Further, to fully support the fact that Novo Nordisk had provided training and briefing to representatives that specifically called out weight as the very reason to prescribe especially against Trulicity, the number 1 selling weekly GLP-1, the complainant required sight of the briefing and training. It

was highly worrying and suspicious that Novo Nordisk would not share this. The complainant urged the PMCPA to examine these materials as a matter of urgency.

The complainant confirmed that the materials shared were the correct materials in question. Nevertheless, the complainant alleged that the campaign spanned beyond the materials shared. Novo Nordisk was trying to detract from the fact that it was promoting Ozempic off label in order to secure the market and set the scene for the imminent launch of oral semaglutide and therefore Novo Nordisk had behaved inappropriately and brought the entire industry into disrepute.

The complainant alleged that details were supplied previously. To summarise, despite the sanctions and two Clause 2 rulings for the exact same reason in 2010/2011, Novo Nordisk had violated the undertaking and was repeating the same mistakes ie promoting Ozempic against its label and denigrating metformin. The complainant was unsure what was unclear as per Novo Nordisk's response with regard to metformin. It was clear that the labels were different and therefore metformin had the legitimate right to be used, therefore promoted, for treating weight loss in type 2 diabetes patients. Clearly Ozempic's label did not have that and Novo Nordisk had been promoting off label. To simplify previous iterations, with regard to weight, metformin's indication (Section 4.1 of the SPC) clearly stated 'Treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone …'. 'A reduction of diabetic complications had been shown in overweight type 2 diabetic patients treated with metformin as first-line therapy after diet failure'; in contrast to Ozempic's indication in Section 4.1, which did not state anything regarding weight unlike the above for metformin.

The complainant alleged that moreover, all of SUSTAIN trials (>10 trials) with greater than ten thousand patients all had metformin as background medication/prerequisite to enter the trial. It was therefore yet again inappropriate to state 'when Metformin was not enough' as metformin was enough in SUSTAIN trials and the effects seen in the trials were in addition to metformin. This was massively misleading especially since the pharmaceutical industry knew how busy GPs/health professionals were and relied heavily on the pharmaceutical industry for education! Novo Nordisk had reduced confidence in the entire pharmaceutical industry and should be reprimanded for this. Therefore, the primary campaign (affecting all Ozempic promotion) stating 'when Metformin was not enough' was denigrating metformin and misleading and claiming off label promotion of Ozempic. Novo Nordisk had denigrated and promoted off label use of not only its product, Ozempic but also metformin by falsely comparing Ozempic to metformin which had a clear weight loss licence in type 2 diabetes. Novo Nordisk claimed that the indication of Ozempic was stated prominently and clearly upfront in all its leavepieces and iDetailer but this was not true even in the pages provided and the materials in question. Section 4.1 clearly referred to glycaemic control and cardiovascular events (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.), which was not stated in any of Novo Nordisk's materials and most certainly not in the pages from the iDetailer. Section 4.1 of the SPC clearly did NOT talk about weight, only glycemia and CV events as mentioned above; therefore, Novo Nordisk had the clear intention to promote off label and mislead health professionals with regards to weight loss promotion.

The complainant alleged that Novo Nordisk's coining the term Diabesity and cross-functional use of signatories with endorsement from senior management, in contrast to the haemophilia business unit, was another clear indication of its intention to brainwash staff and thereby mislead the health community; its signatories clearly required more training.

The complainant alleged that 90% of type 2 diabetes consultation and prescription happened in primary care therefore international reports (not even a guideline) was highly inappropriate. This was a deliberate act to mislead by cherry picking, and thereby not quoting the lead national guideline NICE in Novo Nordisk materials especially the stopping rule, when clearly it chose to refer to it in its response to the PMCPA. NICE could also make recommendations as it saw fit, out with product labels but this was solely their prerogative. Novo Nordisk must still only promote within its licence but it had not as weight was clearly off label and there were disclaimers, or training to that effect, stating that Ozempic was not licensed for weight loss. This was a clear pattern of behaviour exhibiting in Novo Nordisk's history and Novo Nordisk was in breach of Clauses 2 and 3.2.

APPEAL BOARD RULING

The Appeal Board noted that the complainant had the burden of proving his/her complaint on the balance of probabilities. All complaints were judged on the evidence provided by the parties.

The Appeal Board noted that Section 4.1 of the Ozempic SPC stated that 'Ozempic is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise'. In addition, there was mention of study results for glycaemic control and cardiovascular events and that details were in other sections of the SPC. The Appeal Board also noted Novo Nordisk's comments about the regulatory changes in indication for diabetes treatments. References to improvement in glycaemic control were replaced with broader references to insufficiently controlled type 2 diabetes. The Novo Nordisk representatives explained that under regulatory guidance potential medicines had to be either beneficial or neutral with regard to weight.

The Ozempic SPC stated that five trials (SUSTAIN 1–5) had the glycaemic efficacy assessment as the primary objective, while one trial (SUSTAIN 6) had cardiovascular outcome as the primary objective. Section 5.1 of the SPC stated that 'Treatment with semaglutide demonstrated sustained, statistically superior and clinically meaningful reductions in HbA_{1c} and body weight for up to 2 years compared to placebo and active control treatment (sitagliptin, insulin glargine, exenatide ER and dulaglutide)'. Information about the SUSTAIN trials given in the Ozempic SPC included results for primary and secondary endpoints for SUSTAIN 6.

The Appeal Board noted the iDetailer introduction page headline claim 'Help adults with insufficiently controlled type 2 diabetes realise the potential' and then 'Ozempic - a once-weekly GLP-1 RA' treatment with:' 'Superior glycaemic control', 'Superior sustained weight loss' and (separated by a vertical line) 'CV Benefits'. The glycaemic control and weight loss claims were comparisons with dulaglutide, sitagliptin, exenatide OW and insulin glargine U100. The cardiovascular claim was compared to placebo, both in addition to standard of care. Below these claims the indication as set out in Section 4.1 of the SPC was given. There were a number of different sections in the iDetailer. The sections 'Unmet need' and 'Superior Efficacy' included claims with regard to weight. The two leavepieces had similar introduction pages and contained similar weight claims.

The Appeal Board noted the licensed indication for Ozempic was not just for glycaemic control it was for the '**treatment** of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise' (emphasis added). When health professionals prescribed

treatment for patients with insufficiently controlled type 2 diabetes mellitus, weight was a directly relevant factor.

The Appeal Board noted that NICE guidance stated that:

> 'Only continue GLP-1 mimetic therapy if the person with type 2 diabetes had had a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months)'.

The Appeal Board noted from the Novo Nordisk representatives at the appeal that representatives were trained to follow mandatory pages and set any benefits of Ozempic in the context of the licensed indication when on a call with a prescriber. The Appeal Board however considered that the briefing document 'Ozempic Core Launch Guide' should have been clearer regarding the need to ensure that discussions about additional benefits of Ozempic were set within the context of its licensed indication given at Section 4.1 of the SPC. In addition, representatives should be clear with those they called upon that the effect on weight was a secondary endpoint. The Appeal Board was concerned that there was no instruction about which pages were mandatory in the briefing material. Nonetheless the Appeal Board considered that noting Ozempic's broad indication, the treatment of insufficiently controlled type 2 diabetes in certain patients, the introductory pages of the iDetailer and the two leavepieces set out the indication such that the benefit with regard to weight was set within that context.

The Appeal Board noted that the complainant bore the burden of proof and provided little information about what the representative/s had said nor had he/she provided the material at issue.

The Appeal Board considered that the complainant had not shown on the balance of probabilities that the claims regarding weight loss were not presented in the context of the licensed indication for Ozempic. Information about weight loss was included in the SPC. Bearing in mind the limited information provided by the complainant the Appeal Board considered that, irrespective of its comments about the briefing material, in the circumstances the complainant had not shown that Novo Nordisk had promoted Ozempic in a manner which was inconsistent with the particulars listed in its SPC. The Appeal Board therefore upheld the Panel's ruling of no breach of Clause 3.2 in this regard. The appeal on this point was unsuccessful.

The Appeal Board noted its comments above and that of the Panel. The Appeal Board did not consider the circumstances of this case warranted a ruling of a breach of Clause 2 and it upheld the Panel's ruling of no breach of that Clause. The appeal on this point was unsuccessful.

Complaint received **23 September 2019**

Case completed **11 March 2020**