NO BREACH OF THE CODE

CASE AUTH/3686/8/22

COMPLAINANT v ELI LILLY

Allegations regarding a Trulicity email

CASE SUMMARY

This case was in relation to the following three claims within an Eli Lilly and Company Limited Trulicity (dulaglutide) promotional email:

- **Significant HbA1c reduction[1]**
- **Significant weight loss*[1]**
- **Reduction of risk of major adverse cardiovascular (CV) events in both type 2 diabetes**

The Panel ruled no breach of the following Clauses of the 2021 Code because:

- **on balance, it did not consider that in the particular circumstances of this case the complainant had proven, on the balance of probabilities, that failure to state what the improvements in each claim were against, or failure to include information regarding the patients in the trials and statistical significance, was such that the three claims were misleading as alleged**
- **it did not consider that the complainant had established that the claim 'Significant weight loss', a secondary endpoint of the trial, without stating what the primary endpoints of the study were misleading; the claim 'Significant HBA1c reduction' referenced to the same study appeared directly above, the primary endpoint achieved statistical significance and, further, the complainant had not stated why the omission of the primary endpoint, in the particular circumstances of this case, was misleading.**

No Breach of Clause 6.1	**Requirement that claims/information/comparisons must not be misleading**
No Breach of Clause 5.1	**Requirement to maintain high standards at all times**

This summary is not intended to be read in isolation.
For full details, please see the full case report below.

FULL CASE REPORT

A complaint was received from a complainant who described themselves as a concerned health professional about an Eli Lilly and Company Limited Trulicity (dulaglutide) promotional email (ref PP-DG-GB-1212).

Trulicity was indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:

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

COMPLAINT

The complainant provided a screenshot of the email and noted that there were four claims within it.

The email began with 'This promotional content has been developed, organised and funded by Eli Lilly and Company and is intended for UK Healthcare Professionals only. A link to prescribing information and adverse event reporting details are available at the end of the email'. It then included the Trulicity logo alongside an image of a man who appeared to be holding a box of the medicine. Beneath this it stated:

> 'Four reasons to consider Trulicity® (dulaglutide):
>
> When initiating a GLP-1 RA in your patients with type 2 diabetes Trulicity® can be considered. Benefits include:
>
> - Significant HbA1c reduction[1]
> - Significant weight loss*[1]
> - Reduction of risk of major adverse cardiovascular (CV) events in both type 2 diabetes primary and secondary CV prevention population[2].
> - Once-weekly dosing[3,4], a ready-to-use pen with a small pre-attached, hidden needle.
>
> **Trulicity is not indicated for weight loss. In clinical trials, weight change was a secondary end point [4].*

This was followed by a box inviting readers to learn more about Trulicity followed by its indication and the most frequently reported adverse reactions for Trulicity which were gastrointestinal, including nausea, vomiting and diarrhoea followed by the list of references and then a link to the prescribing information and a box including the adverse event reporting details.

The complainant stated that the first three claims were about the company's product but the complainant was unclear what this improvement was against, was it versus no treatment at all or against standard of care (which was what?). There was also no information regarding the patients in the trial – be that their initial features or even the number of patients. Statistical significance was also not provided. On the [third] claim, this was made clear that this was a second endpoint of the trial, but there was nothing that stated what the primary endpoints of the study were.

When writing to Eli Lilly, the Authority asked it to consider the requirements of Clauses 5.1 and 6.1 of the 2021 Code.

RESPONSE

Eli Lilly noted that the complaint concerned a promotional email for Trulicity (dulaglutide), which was no longer in use, and which was sent to UK health professionals, via a named third party , who had subscribed to receive content from it along with promotional content from third parties.

The purpose of the email was to draw attention to the key attributes of Trulicity, all of which were consistent with the Trulicity summary of product characteristics (SPC) and were collectively substantiated by the references. Eli Lilly believed that these, together with details of the most frequently reported adverse reactions, were sufficiently complete to enable recipients to form their own opinion of the therapeutic value of Trulicity. Each of the four claims referred to by the complainant were factually accurate and complete as standalone statements and were substantiated by the references cited.

The complainant stated that they were unclear as to what the comparator was for the first three claims. However, these statements were not comparative and none of them contained a comparative adjective. Therefore, Eli Lilly believed that it would be intuitively obvious to its intended audience (ie, those familiar with the management of type 2 diabetes) that these statements referred to effects of Trulicity on relevant clinical parameters versus baseline.

Eli Lilly believed that the information provided to the recipient was accurate, non-comparative and sufficiently complete to enable recipients to form their own opinion of the therapeutic value of Trulicity. Each claim, therefore, met the requirements of Clause 6.1.

Eli Lilly noted that the complainant referred to the third claim alleging that it indicated a secondary endpoint without referring to the primary endpoint of the study. The point 'Reduction of risk of major adverse cardiovascular (CV) events in both a type 2 diabetes primary and secondary CV prevention population' was a primary endpoint and, therefore, Eli Lilly were interpreting this as referring to the qualifying statement for significant weight loss (point 2 of 4) that was provided for transparency immediately below the claims.

The primary endpoint in all Trulicity efficacy trials (with the exception of the cardiovascular outcome study) was HbA1c lowering; this would be understood by health professionals with an interest in diabetes since it was a regulatory requirement, it was consistent with other treatments for the management of people with type 2 diabetes and reflected by the ordering of the attributes.

It was also widely understood by diabetes clinicians that weight reduction was a secondary benefit associated with the use of GLP-1 receptor agonists. This benefit was extremely relevant to the diabetes population and so was important to highlight to prescribers. However, since there were also GLP-1 RAs that were specifically licensed for weight reduction (eg, semaglutide), Eli Lilly added this point immediately below the claims to be very clear that Trulicity was not specifically indicated for this use. Eli Lilly pointed out that weight change was a secondary endpoint in trials so that readers could understand that it had been studied, that it was a 'secondary benefit'.

Therefore, Eli Lilly had not cited a secondary endpoint without referring to the primary endpoint, as alleged. On this point, Eli Lilly did not consider that the material was in breach of Clause 6.1, rather that the added information about weight loss made the claim sufficiently complete to allow a proper assessment of its therapeutic value.

Eli Lilly did not believe that the promotional email at issue was in breach of Clause 6.1 and, therefore, not in breach of Clause 5.1.

PANEL RULING

The Panel noted that the email was headed 'Four reasons to consider Trulicity (dulaglutide):'. Beneath, in less prominent typeface, it stated 'When initiating a GLP-1RA in your patients with type 2 diabetes Trulicity can be considered. Benefits include:', above a list of 4 benefits.

The Panel noted that the first two claims regarding the benefits offered by Trulicity, namely 'Significant HBA1c reduction' and 'Significant weight loss', were both referenced to Frias *et al* (2022) which was a randomised controlled dose escalation trial (AWARD-II) comparing the efficacy and safety of dulaglutide at doses of 3.0 and 4.5 mg versus 1.5 mg in patients with type 2 diabetes inadequately controlled with metformin. The primary objective was determining superiority of dulaglutide 3.0 mg and/or 4.5 mg over 1.5 mg in change in HbA1c from baseline at 36 weeks. All treatment doses were efficacious using the treatment-regimen estimand (HbA1c least-square mean [LSM] change from baseline at 36 weeks, 21.54% for 1.5 mg, 21.64% for 3.0 mg, and 21.77% for 4.5 mg). Secondary superiority objectives included change from baseline in body weight. At 36 weeks, dulaglutide 4.5 mg provided superior HbA_{1c} reductions compared with 1.5 mg (treatment-regimen estimand: -1.77 vs. -1.54% [-19.4 vs.-16.8 mmol/mol], estimated treatment difference [ETD] -0.24% (-2.6 mmol/mol), P < 0.001; efficacy estimand:-1.87 vs. -1.53% [-20.4 vs.-16.7 mmol/mol], ETD -0.34% (-3.7 mmol/mol), P < 0.001). Dulaglutide 3.0 mg was superior to 1.5 mg for reducing HbA_{1c}, using the efficacy estimand (ETD -0.17% [-1.9 mmol/mol]; P = 0.003) but not the treatment-regimen estimand (ETD -0.10% [-1.1 mmol/mol]; P = 0.096). Dulaglutide 4.5 mg was superior to 1.5 mg for weight loss at 36 weeks for both estimands (treatment regimen: -4.6 vs. -3.0 kg, ETD -1.6 kg, P < 0.001; efficacy: -4.7 vs. -3.1 kg, ETD -1.6 kg, P < 0.001). Superiority of the 3.0-mg dose on body weight could not be formally tested using the treatment-regimen estimand in the graphical testing method because this dose did not achieve superiority on the primary HbA1c end point. However, a pattern of dose-related decrease in body weight was observed at 36 weeks and 52 weeks. The study concluded that in patients with type 2 diabetes inadequately controlled by metformin, escalation from dulaglutide 1.5 mg to 3.0 mg or 4.5 mg provided clinically relevant, dose-related reductions in HbA1c and body weight with a similar safety profile.

The third claim 'Reduction of risk of major adverse cardiovascular (CV) events in both a type 2 diabetes primary and secondary CV prevention population' was referenced to Gerstein *et al* (2019), which was a multicentre, randomised, double-blind, placebo-controlled trial (REWIND) in which the effect of the GLP-1 receptor agonist dulaglutide on major adverse cardiovascular events when added to the existing antihyperglycaemic regimens of individuals with type 2 diabetes with and without previous cardiovascular disease and a wide range of glycaemic control was assessed. The primary endpoint was the first occurrence of any component of the composite outcome, which comprised non-fatal myocardial infarction, non-fatal stroke, and death from cardiovascular causes or unknown causes. The trial of 9,901 people had a long median follow-up period of 5·4 years, recruited a low proportion of people (31.5%) with previous cardiovascular disease, a high proportion of women (46.3%), and followed people with a mean HbA1c of 7.3%. Findings showed that weekly injections of the GLP-1 receptor agonist dulaglutide reduced cardiovascular outcomes in both men and women with or without previous cardiovascular disease, and had an effect size similar to that observed in the other GLP-1 receptor agonist cardiovascular outcomes trials. Implications of all the available evidence GLP-1 receptor agonists that have been shown to reduce cardiovascular outcomes should be considered for the management of glycaemic control in people with type 2 diabetes with either previous cardiovascular disease or cardiovascular risk factors.

The Panel noted Eli Lilly's submission that the three claims highlighted by the complainant were not comparative and it would be intuitively obvious to its intended audience (ie, those familiar with the management of type 2 diabetes) that these statements referred to effects of Trulicity on relevant clinical parameters versus baseline. The Panel noted that, according to the certificate, the target audience was HCP, Pharmacist, Physician, Nurse and the email was sent to those health professionals who had 'marked their interest in Diabetes', and queried whether all within that cohort would be familiar with the management of diabetes as submitted by Eli Lilly. In addition, the Panel noted that the email could be accessed by all health professionals on the third party health professional list using certain search terms. The Panel noted that neither of the two studies referenced included any comparator products, although this was not made clear in the email. The Panel considered that the subheading 'When initiating a GLP-1RA in your patients with type 2 diabetes Trulicity can be considered' implied that other products within the class were available and this would have been apparent in any event to those recipients that were familiar with diabetes management.

Whilst the Panel considered that it might have been helpful to provide further details in the main body of the email about the studies cited, it noted that none of the bullet points were comparative. The Panel noted that a short description of the studies was included in the reference list which highlighted that Frias *et al* only included different doses of dulaglutide and Gerstein *et al* was a placebo-controlled trial.

On balance, the Panel did not consider that in the particular circumstances of this case the complainant had proven, on the balance of probabilities, that failure to state what the improvements in each claim were against, or failure to include information regarding the patients in the trials and statistical significance, was such that the three claims were misleading, as alleged, and **no breach of Clause 6.1** was ruled in relation to each claim.

Nor did the Panel consider that the complainant had established that the claim 'Significant weight loss', a secondary endpoint of the trial, without stating what the primary endpoints of the study were misleading. The Panel noted that the claim 'Significant HBA1c reduction' referenced to the same study appeared directly above. The Panel noted that the primary endpoint achieved statistical significance and, further, the complainant had not stated why the omission of the primary endpoint, in the particular circumstances of this case, was misleading. The Panel therefore ruled **no breach of Clause 6.1** in this regard.

The Panel noted its rulings above and consequently ruled **no breach of Clause 5.1**.

Complaint received **18 August 2022**

Case completed **9 October 2023**