CASE AUTH/2948/3/17

GENERAL PRACTITIONER v NOVO NORDISK

Promotion of Tresiba

A general practitioner complained about a Tresiba (insulin degludec) email sent by Novo Nordisk.

The start of the email included the claims 'Get HbA1c DOWN with CONTROL' and 'NEW LOWER PRICE'. It gave details of a price reduction followed by 'You might be surprised by Tresiba treatment cost (Type 2 Basal only)'. The email then referred to a recent 35% price reduction and that studies in basal insulin had demonstrated that patients required a 10% lower insulin dose on Tresiba vs insulin glargine U100 (p= 0.0004) referenced to Vora *et al* 2015. This was followed by an asterisk which was explained beneath a comparison table as 'Type 2 Diabetes (basal oral): Tresiba = 0.39u/kg vs insulin glargine U100 = 0.43u/kg'. The next claim was that patients required a 17% higher insulin dose on insulin glargine U300 vs insulin glargine U100 referenced to Bolli *et al* 2015. This was followed by another symbol which was also explained beneath the comparison table as 'Absolute daily basal dose at end of trial: insulin glargine U300 = 0.62u/kg vs insulin glargine U100 = 0.53u/kg'.

A table then compared an illustrative dose (U), monthly cost and annual cost of Tresiba U100, Tresiba U200, Toujeo, (insulin glargine pre-filled pen; Sanofi), Lantus (insulin glargine; Sanofi) and Abasaglar (insulin glargine; Eli Lilly). At the doses chosen, Toujeo was the most expensive at £34.96 per month, then Tresiba (both U100 and U200 cost £34.04 per month), Lantus (£33.68) and Abasaglar (£28.64).

Tresiba was indicated for the treatment of diabetes mellitus. It was a basal insulin for once-daily administration.

The complainant took exception to the email as he had never given Novo Nordisk permission to send promotional material.

The complainant was concerned that the cost comparison chart which compared Tresiba with Lantus, Abasaglar and Toujeo was not evidenced based as there were no published clinical trials that directly compared Tresiba with the other insulins shown in the chart particularly given the lack of clinical evidence to demonstrate dose for dose equivalence on HbA1c effect.

Also the title, 'You might be surprised by Tresiba treatment cost (Type 2 Basal only)' seemed to relate only to type 2 basal diabetics. However, the studies used to make comparisons included type 1 diabetics. In addition it was not clear what was meant by the claim 'Successful reductions' and what comparison it was trying to make.

The detailed response from Novo Nordisk is given below.

The Panel considered that on the information provided by Novo Nordisk, in the absence of an agreement from the complainant to be identified to Novo Nordisk, there was no evidence before the Panel to establish whether the complainant had given permission to receive promotional emails. The Panel thus ruled no breach of the Code.

The Panel noted that the cost comparison table in the email was followed by an explanation of the doses used. It appeared that the primary messages from the email, were that there was a 35% price reduction across all Tresiba presentations and that this reduced treatment cost compared favourably to other insulins in relation to treatment of type 2 diabetes. The prominent cost comparison table stated an illustrative dose and invited readers to directly compare the monthly and annual costs of Tresiba, Toujeo, Lantus and Abasaglar. In the Panel's view, the initial impression might be that there was direct comparative data, and that was not so. In the absence of such comparative data, the basis of the comparison should be made clear. In this regard, text three paragraphs beneath the table read 'Assumed illustrative dose for IGlar of 40U/ day. Comparable annual treatment costs calculated using dose ratios from the BEGIN meta-analysis, the EDITION 3 trial (for glargine U300), Toujeo SmPC and Abasaglar SmPC'. This was followed by further explanation of the costs etc and then the prominent claim 'Tresiba is now at a comparable treatment cost to glargine U100 (Lantus) and glargine U300 in type 2 diabetes patients treated with basal only therapy' referenced to Vora *et al*, Bolli *et al* and MIMS December 2016. Two highlighted boxes then followed, one referred to the 35% price reduction and the second to the Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG) approvals for use in type 1 and type 2 diabetics. Three bullet points concluded the email, the first read 'Successful reductions in HbA1c', referenced to Rodbard *et al* 2013 and Bode *et al* 2013.

Vora *et al* was a meta-analysis of Tresiba and glargine in type 1 and type 2 diabetes mellitus (basal-bolus treated type 1, insulin naïve type 2 and basal-bolus treated type 2). The conclusions included that insulin naïve type 2 patients treated with Tresiba needed lower total doses of insulin than those treated with glargine. The results showed that the total daily dose at the end of trial was 10% lower (p=0.0004) with Tresiba in type 2 diabetic insulin naïve patients (end of trial dose Tresiba 0.39U/kg and glargine 0.43U/kg). In basal-bolus type 2 diabetic patients the total daily insulin dose did not differ statistically between treatments (Tresiba 1.22U/kg and glargine 1.18U/kg).

Bolli *et al* compared the safety and efficacy of glargine 300U with glargine 100U in insulin naïve patients with type 2 diabetes.

The SPC for Toujeo stated that when switching from insulin glargine 100U to Toujeo this could be done on a unit-to-unit basis but a higher Toujeo dose (approximately 10-18%) might be needed to achieve target ranges for plasma glucose levels.

The Panel was concerned that the data in the cost comparison was from a number of trials. Tresiba was not compared with each medicine mentioned, for example the comparison with Toujeo was based on two comparisons between Toujeo and Lantus and the other between Tresiba and Lantus.

The Panel noted that the data used in the comparison table were from type 2 patients only on basal insulin and derived from two studies. In these circumstances, the Panel did not consider it was misleading to reference the comparisons in the table to Vora *et al* which also investigated type 1 patients. Thus the Panel ruled no breach of the Code on this narrow point.

The Panel noted its comments above about the comparison chart. The first two paragraphs beneath the comparison table related to, and qualified, the dose claims above the table rather than the data in the table. The third paragraph which was in less prominent font than the two paragraphs that immediately preceded it sought to explain the data in the comparison table. In the Panel's view, the assumptions used for the illustrative doses were not sufficiently complete or prominent. The Panel considered that the comparison table was misleading and ruled breaches of the Code.

The claim 'Successful reductions in HbA1C' appeared beneath two highlighted boxes, one of which referred to type 1 and type 2 diabetes. Above the highlighted boxes was the prominent comparative claim about treatment costs for Tresiba in type 2 diabetes compared to glargine. It was not clear whether the following three bullet points including 'Successful reductions in HbA1c' related to type 1 and type 2 diabetes. However, Tresiba was indicated for use in both conditions and both conditions were referred to in the box immediately above. The referenced studies Rodbard *et al* was in type 2 diabetes patients and Bode *et al* 2013 was in type 1 diabetes patients. The Panel did not accept Novo Nordisk's submission that the prominent comparative claim vs Lantus and glargine U300 summarized the information presented in the first section. Visually it sat immediately above the highlighted boxes and, in the Panel's view, its prominence, position, green font and design gave the context for the claims beneath. The claim 'Successful reductions in HbA1c' might be read as applying to all three products, others might read it as a benefit for Tresiba compared to Lantus and glargine U300. There was some relevant data in Rodbard *et al* and Bode *et al*. Nonetheless, and on balance, it was not sufficiently clear. Breaches of the Code were ruled.

In relation to the allegation that it was not clear what was meant by 'Successful reductions in HbA1c', the Panel noted Novo Nordisk's submission about treat-to-target trials and their primary endpoints. The Panel did not consider the claim misleading on this point as alleged. The Panel did not consider that it was misleading to reference the claim to studies on both type 1 and type 2 patients given the reference to such patients in the box immediately above. The Panel ruled no breaches of the Code including that the company had not failed to maintain high standards.

A general practitioner complained about a Tresiba (insulin degludec) email (ref UK/TB/1116/0498) sent by Novo Nordisk Ltd.

The start of the email included claims 'Get HbA1c DOWN with CONTROL' and 'NEW LOWER PRICE'. It referred to a price reduction from £72 to £46.60 (5 x 3mL 100U/mL Penfill/FlexTouch) and from £86.40 to £55.92 (3 x 3ml 200U/mL FlexTouch) on 1 July 2016. This was followed by 'You might be surprised by Tresiba treatment cost (Type 2 Basal only)'. The email then referred to the recent 35% price reduction and that studies in basal insulin had demonstrated that patients required a 10% lower insulin dose on Tresiba vs insulin glargine U100 (p= 0.0004) referenced to Vora *et al* 2015. This was followed by an asterisk which was explained beneath a comparison table as 'Type 2 Diabetes (basal oral): Tresiba = 0.39u/kg vs insulin glargine U100 = 0.43u/kg'. The next claim was that patients required a 17% higher insulin dose on insulin glargine U300 vs insulin glargine U100 referenced to Bolli *et al* 2015. This was followed by another symbol which was also explained beneath the comparison table as 'Absolute daily basal dose at end of trial: insulin glargine U300 = 0.62u/kg vs insulin glargine U100 = 0.53u/kg'.

A table then compared an illustrative dose (U), monthly cost and annual cost of Tresiba U100, Tresiba U200, Toujeo, Lantus and Abasaglar. At the doses chosen, Toujeo was the most expensive at £34.96 per month, then Tresiba (both U100 and U200 cost £34.04 per month), Lantus (£33.68) and Abasaglar (£28.64).

Tresiba was indicated for the treatment of diabetes mellitus and was available in 100 units/ml (U100) and 200 units/ml (U200). It was a basal insulin for once-daily administration preferably at the same time every day.

COMPLAINT

The complainant explained that the mailer had been sent to his practice's email account. He usually took little notice of pharmaceutical company promotional mailers sent in the post. However, in this case he had taken exception to the material at issue because it was sent by email although he had never given Novo Nordisk permission to send him such promotional material which was annoying. Also the complainant took issue with a number of misleading messages made in comparison to a number of established treatments that his practice commonly used to manage its insulin dependent diabetics.

The complainant stated that he had discussed the material with colleagues. There were shared significant concerns that the cost comparison chart which compared Tresiba with Lantus (insulin glargine; Sanofi), Abasaglar (insulin glargine; Eli Lilly) and Toujeo (insulin glargine pre-filled pen; Sanofi) was not evidenced based as there were no published clinical trials that directly compared Tresiba with the other insulins shown in the chart. The complainant did not understand how Novo Nordisk could make fair cost comparisons with these other insulins given the lack of clinical evidence to demonstrate dose for dose equivalence on HbA1c effect.

Also the title on the material, 'You might be surprised by Tresiba treatment cost (Type 2 Basal only)' seemed to relate only to type 2 basal diabetics. However, the studies used to make comparisons included studies that were in type 1 diabetics which was a very different patient population. The first reference, Vora *et al* (2014), contained studies in a large number of type 1 patients. The referenced publications used to support 'Successful reductions in HbA1c' (Rodbard *et al* 2013 and Bode *et al* 2013) were also for type 1 diabetics although the messages seemed to be related only to type 2 diabetics. In addition it was not clear what was meant by the claim 'Successful reductions' and what comparison it was trying to make. The complainant stated that in his practice, over 90% of diabetic patients had type 2 diabetes and therefore the material should be relevant to that patient type and not be misleading by including in type 1 patients; in the complainant's view this seemed very underhand and manipulative of Novo Nordisk.

When writing to Novo Nordisk the Authority asked it to consider the requirements of Clauses 7.2, 7.3, 7.4, 9.1 and 9.9 of the Code.

RESPONSE

Novo Nordisk explained that the email was sent on 22 December 2016 by a third party mailing house. The recipients were health professionals who had given their consent to receive such emails and who had an interest in diabetes to include diabetologists/endocrinologists, GPs with a specialist interest in diabetes, diabetes specialist nurses, GPs and practice nurses. The email was re-sent on 19 January 2017 to those who had not opened the first email.

The database of recipients used by the mailing house was described. Recipients of the email had provided their consent to receive promotional emails from pharmaceutical companies via a robust 4 stage process:

1 A representative of the database company telephoned the health professional to verify contact details and to confirm if he/she would like to be a member of the database. The nature of the service described included receiving emails from its associated/affiliated companies and their products and services, which might include pharmaceutical promotional materials.

2 The health professional was then sent a registration email with an access code to complete the registration form online. When completing their online registration form, a statement clearly informed the health professional that by completing the form he/she was agreeing to the terms and conditions which were clearly accessible as part of the online registration process. The email stated the following: '[the database company] will from time to time send information by email about our associated/affiliated companies, and their clients' product and services. This may include updates on specialist services, conferences and seminars, diagnostic, medical and pharmaceutical promotional materials as well as official information'.

3 The terms and conditions included the opt-in policy, which clearly stated that information provided might include pharmaceutical promotional materials and that users could opt out of receiving such materials without losing the remainder of the service. The health professional had to tick a box to confirm agreement with the terms and conditions before registration could be completed. Once the registration form was complete, the health professional was sent a confirmation email.

4 Health professionals were telephoned annually to confirm and update (if required) the information held. During this process, they were reminded that they had consented to receive emails from the database company or its associated/affiliated companies, which included promotional information from pharmaceutical companies.

With regard to the complainant's concerns about the cost comparison chart, Novo Nordisk submitted that treatment cost of insulin therapy was affected by not just the acquisition cost but also the daily required dose of insulin. The purpose of the cost comparison chart was to demonstrate this. The actual required dose of any insulin was of course individualised, however, the World Health Organisation (WHO) defined daily dose (DDD) of 40 units was regularly used as the reference point.

Bolli *et al* (2015) compared Toujeo with Lantus and showed that patients receiving Toujeo required on average a dose of 0.62U/kg, whilst those on Lantus required a dose of 0.53U/Kg, equating to a 17% higher insulin dose requirement for Toujeo over Lantus. If the WHO DDD of 40 units of Lantus was used as the reference point, a 17% higher insulin dose equated to 46.8U/kg of Toujeo. The same methodology could be applied for Tresiba based on the pre-specified type 2 basal only meta-analysis of the BEGIN trials (Vora *et al*), where it was shown that on average, patients required a 10% lower insulin dose of Tresiba vs Lantus. Again if 40 units of Lantus was used as the reference point, this equated to 36 units of Tresiba. Tresiba U100 and U200 had been shown to have bioequivalence as had Lantus and Abasaglar, therefore the same doses had been applied to these respective insulins.

The comparison of Tresiba vs glargine U100 was supported by Vora *et al* and the comparison of Toujeo

vs glargine U100 was supported by Bolli *et al* and the Toujeo summary of product characteristics (SPC).

With regard to the complainant's concerns about the use of data from type 1 diabetics, Novo Nordisk stated that Vora *et al* and Bolli *et al* were used to reference the cost comparison chart; none of the other references used within the mailer related to the chart. While the meta-analysis by Vora *et al* included both type 1 and type 2 patient data, only type 2 basal only insulin data had been used to substantiate the information in the chart. Bolli *et al* referred to the EDITION 3 trial which only related to the type 2 basal only insulin population.

The claim 'Tresiba is now at a comparable treatment cost to glargine U100 (Lantus) and glargine U300 in type 2 diabetes patients treated with basal insulin alone therapy' was positioned to summarise the information presented within the first section of the mailer which related to the cost of basal insulins in the type 2 basal only market. The next section of the mailer was separated into two boxes, both of which related to the use of Tresiba in patients with type 1 or type 2 diabetes and provided information on the general 35% price reduction (left-hand box) and the approval status of Tresiba with the All Wales Medicines Strategy Group (AWMSG) and the Scottish Medicines Consortium (SMC) (right-hand box). The final statements provided the key messages for Tresiba which understandably for an insulin product related to patients with either type 1 or type 2 diabetes. As such Novo Nordisk submitted that it was appropriate to reference the first key claim ('Successful reductions in HbA1c') to both Rodbard *et al* (type 2 diabetes patients) and Bode *et al* (type 1 diabetes patients).

Novo Nordisk submitted that the claim 'Successful reductions' did not make any comparison but simply underlined the successful improvement in glycaemic control demonstrated by confirmatory trials. This claim was supported by treat-to-target trials used as reference. The very notion of treat-to-target trials for insulin implied no difference in glycaemic control between the two comparators; hence the overall improvement in HbA1c was the primary endpoint of confirmatory trials.

Based on the above, Novo Nordisk submitted that the content of the mailer and its distribution met the requirements of Clauses 7.2, 7.3, 7.4, 9.1 and 9.9.

PANEL RULING

The Panel noted that the complainant stated that he/she wished to remain anonymous. The case preparation manager had not asked the complainant for permission to identify him/her to Novo Nordisk so that the company could investigate the allegation that the complainant had not given Novo Nordisk permission to send promotional material by email. The Panel noted the explanation from Novo Nordisk about the database used to send the material and that recipients had provided consent to receive promotional emails from pharmaceutical companies. The Panel noted that recipients were also contacted annually to validate the information held. The Panel noted the circumstances and considered that on the information provided by Novo Nordisk, in the absence of an agreement from the complainant to be identified to Novo Nordisk, there was no evidence before the Panel to establish whether the complainant had given permission to receive promotional emails. The Panel thus ruled no breach of Clause 9.9 of the Code.

The Panel noted that the cost comparison table in the email was followed by an explanation of the doses used. It appeared that the primary messages from the email, which appeared in green font or against a prominent green background, were that there was a 35% price reduction across all Tresiba presentations and that this reduced treatment cost compared favourably to other insulins in relation to treatment of type 2 diabetes. The prominent cost comparison table stated an illustrative dose and invited readers to directly compare the monthly and annual costs of Tresiba U100, U200, Toujeo, Lantus and Abasaglar. In the Panel's view, the initial impression given to some readers might be that there was direct comparative data, as stated by the complainant, and that was not so. In the absence of such comparative data, the basis of the comparison should be made clear and be an integral part of the table or sufficiently prominent such that it was with the table's visual field. In this regard, text three paragraphs beneath the table read 'Assumed illustrative dose for IGlar of 40U/day. Comparable annual treatment costs calculated using dose ratios from the BEGIN meta-analysis, the EDITION 3 trial (for glargine U300), Toujeo SmPC and Abasaglar SmPC'. This was followed by further explanation of the costs etc and then the prominent claim 'Tresiba is now at a comparable treatment cost to glargine U100 (Lantus) and glargine U300 in type 2 diabetes patients treated with basal only therapy' referenced to Vora *et al*, Bolli *et al* and MIMS December 2016. Two highlighted boxes then followed, one referred to the 35% price reduction and the second to the Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG) approvals for use in type 1 and type 2 diabetics. Three bullet points concluded the email, the first read 'Successful reductions in HbA1c', referenced to Rodbard *et al* 2013 and Bode *et al* 2013.

Vora *et al* was a meta-analysis of Tresiba and glargine in type 1 and type 2 diabetes mellitus (basal-bolus treated type 1, insulin naïve type 2 and basal-bolus treated type 2). The conclusions included that insulin naïve type 2 patients treated with Tresiba needed lower total doses of insulin than those treated with glargine. The results showed that the total daily dose at the end of trial was 10% lower (p=0.0004) with Tresiba in type 2 diabetic insulin naïve patients (end of trial dose Tresiba 0.39U/kg and glargine 0.43U/kg). In basal-bolus type 2 diabetic patients the total daily insulin dose did not differ statistically between treatments (Tresiba 1.22U/kg and glargine 1.18U/kg). The units per kg were adjusted for covariates (estimated using ANOVA with treatment, sex, antidiabetic therapy at screening, age and baseline dose as covariates).

Bolli *et al* compared the safety and efficacy of glargine 300U with glargine 100U in insulin naïve patients with type 2 diabetes. Participants were

receiving oral glucose-lowering medicines for at least 6 months prior to screening. Insulin dose was adjusted once weekly.

The SPC for Toujeo stated in Section 4.2 that when switching from insulin glargine 100U to Toujeo this could be done on a unit-to-unit basis but a higher Toujeo dose (approximately 10-18%) might be needed to achieve target ranges for plasma glucose levels.

The Panel was concerned that the data in the cost comparison was from a number of trials. Tresiba was not compared with each medicine mentioned, for example the comparison with Toujeo was based on two comparisons between Toujeo and Lantus and the other between Tresiba and Lantus. Bolli *et al* aimed at achieving pre-breakfast plasma glucose 4.4-5.6mmol/L (80-100mg/di). Vora *et al* also used treat to target of self-measured blood glucose <5mmol/L.

The Panel noted that the data used in the comparison table were from type 2 patients only on basal insulin and derived from Vora *et al* and Bolli *et al*. In these circumstances, the Panel did not consider it was misleading to reference the comparisons in the table to Vora *et al* which also investigated type 1 patients. Thus the Panel ruled no breach of Clause 7.2 on this narrow point.

The Panel noted its comments above about the comparison chart. The first two paragraphs beneath the comparison table related to, and qualified, the dose claims above the table rather than the data in the table. The third paragraph which was in less prominent font than the two paragraphs that immediately preceded it sought to explain the data in the comparison table. In the Panel's view, the assumptions used for the illustrative doses were not sufficiently complete or prominent. The Panel considered that the comparison table was misleading and the Panel ruled breaches of Clauses 7.2 and 7.3 of the Code.

The claim 'Successful reductions in HbA1C' appeared beneath two highlighted boxes, one of which referred to type 1 and type 2 diabetes. Above the highlighted boxes was the prominent comparative claim about treatment costs for Tresiba in type 2 diabetes compared to glargine U100 and U300. It was not clear whether the following three bullet points including 'Successful reductions in HbA1c' related to type 1 and type 2 diabetes. However, Tresiba was indicated for use in both conditions and both conditions were referred to in the box immediately above. The referenced studies Rodbard *et al* was in type 2 diabetes patients and Bode *et al* 2013 was in type 1 diabetes patients. The Panel did not accept Novo Nordisk's submission that the prominent comparative claim vs Lantus and glargine U300 summarized the information presented in the first section. Visually it sat immediately above the highlighted boxes and, in the Panel's view, its prominence, position, green font and design gave the context for the claims beneath. The claim 'Successful reductions in HbA1c' might be read as applying to all three products others might read it as a benefit for Tresiba compared to Lantus and glargine U300. There was some relevant data in Rodbard *et al* and Bode *et al*. Nonetheless, and on balance, it was not sufficiently clear. A breach of Clauses 7.2 and 7.3 was ruled.

In relation to the allegation that it was not clear what was meant by 'Successful reductions in HbA1c', the Panel noted Novo Nordisk's submission about treat-to-target trials and their primary endpoints. The Panel did not consider the claim misleading on this point as alleged. No breach of Clause 7.2 was ruled. The Panel did not consider that it was misleading to reference the claim to studies on both type 1 and type 2 patients given the reference to such patients in the box immediately above. The Panel ruled no breach of Clauses 7.2 and 7.3 of the Code.

The Panel noted its rulings above and, on balance, considered that the company had not failed to maintain high standards. No breach of Clause 9.1 was ruled.

Complaint received **22 March 2017**

Case completed **21 July 2017**