CASE AUTH/3062/8/18

HEALTH PROFESSIONAL v SANOFI

Toujeo leaflet

A consultant physician complained about a six-page A5 gate-folded leavepiece produced by Sanofi. The leavepiece related to Toujeo (insulin glargine 300 units/mL) which was indicated for the treatment of diabetes mellitus in adults.

The complainant was concerned that the leavepiece misrepresented a clinical trial. He/she was not suggesting any factual errors; however, he/she considered the leavepiece, describing a study that compared Toujeo with insulin degludec, misleading. The complainant alleged that the leavepiece highlighted results from the titration period which appeared to favour Sanofi's product. These were presented graphically over two prominent pages. According to the complainant, the overall results of the study, which showed no difference between the two insulins, appeared only in text on a 'back page' of the leavepiece and stated, 'Comparable incidence and event rates of anytime and nocturnal hypoglycaemia in the maintenance and full 24-week study periods'. The complainant estimated that this took up around 5% of the space devoted to the results from the titration period, as well as having a much less prominent position. The complainant stated that the hypoglycaemia rate during 0-12 weeks was not described as a primary or secondary endpoint, only featured as one of three safety endpoints and was not mentioned on clinicaltrials.gov. The complainant alleged that Sanofi produced misleading promotional material which placed undue emphasis on favourable results from a safety endpoint obtained from 12 weeks of a 24-week study, with only brief mention of the overall results of the study.

The detailed response from Sanofi is given below.

The Panel noted that the leavepiece solely discussed the BRIGHT study (Rosenstock *et al*, 2018). The BRIGHT study was a head-to-head 24-week study which demonstrated non-inferiority of Toujeo vs insulin degludec for the primary endpoint; HbA1c change from baseline to week 24. The Panel noted Sanofi's submission that pre-specified safety endpoints included the incidence and event rates of hypoglycaemia during the 24-week on-treatment period, which consisted of the active titration period (weeks 0-12), and the maintenance period (weeks 13-24).

The Panel noted that the safety endpoints, hypoglycaemia incidence and event rates (anytime and nocturnal) over 24 weeks, were comparable with both insulins. The Panel noted the clinical relevance of the hypoglycaemia data during the titration period. The Panel considered that it was not unreasonable to present secondary endpoint data, nor was it unreasonable to present such data from the titration period, if it was presented in the context of the full study period and with proportionate emphasis. The Panel acknowledged the bullet points referencing comparable hypoglycaemia incidence and event rates during the maintenance and 24-week study periods at the bottom of the middle and third inside pages and as the second bullet point on the summary back page. In the Panel's view, a single bullet point at the bottom of the middle and third inside pages was disproportionate to the prominent graphical representation of the titration period data which occupied most of those pages; insufficient weight had been given to the hypoglycaemia results for the full 24-week treatment period, which were comparable between the treatment arms. The Panel considered the immediate impression to a busy health professional; in the Panel's view, the titration period hypoglycaemia results were designed to be the primary take home message of the leavepiece. The leavepiece predominately highlighted the hypoglycaemia results during the 12-week titration period, which favoured Toujeo, without sufficient balance. The Panel considered that the leavepiece placed disproportionate emphasis on the results that had favoured Sanofi's product and, in that regard, misrepresented the study and the immediate impression was a misleading comparison of the two insulins. Breaches of the Code were ruled.

A consultant physician complained about a six-page A5 gate-folded leavepiece (SAGB.TJO.18.06.0924(1)) produced by Sanofi. The leavepiece related to Toujeo (insulin glargine 300 units/mL) which was indicated for the treatment of diabetes mellitus in adults.

COMPLAINT

The complainant was concerned that the leavepiece misrepresented a clinical trial. He/she was not suggesting any factual errors; however, he/she considered the leavepiece, describing a study that compared Toujeo with insulin degludec, misleading. The study consisted of two phases: an initial 12-week titration period during which insulin doses were adjusted, followed by a second 12-week period during which doses could be adjusted, if necessary, but without this being a specific target. The complainant alleged that the leavepiece highlighted results from the titration period which appeared to favour Sanofi's product. These were presented graphically over two prominent pages. According to the complainant, the overall results of the study, which showed no difference between the two insulins, appeared only in text on a 'back page' of the leavepiece and stated, 'Comparable incidence and event rates of anytime and nocturnal hypoglycaemia in the maintenance and full 24-week study periods'. The complainant estimated that this took up around

5% of the space devoted to the results from the titration period, as well as having a much less prominent position.

The complainant highlighted the study endpoints from the BRIGHT study which he/she reproduced below and noted that the hypoglycaemia rate during 0-12 weeks was not described as a primary or secondary endpoint, and only featured as one of three safety endpoints.

- The primary endpoint was the change in HbA1c from baseline to week 24.
- Secondary efficacy endpoints included change in fasting plasma glucose (FPG), fasting self-measured plasma glucose (SMPG), and eight-point SMPG profiles from baseline to week 24; change in variability of 24-h SMPG, based on eight-point profiles; percentage of participants reaching target HbA1c <7.0% (<53 mmol/mol) at week 24; and percentage of participants reaching target HbA1c <7.0% (<53 mmol/mol) at week 24 without confirmed hypoglycaemia (<70 mg/dL and <54 mg/dL) during the 24-week treatment period.
- Safety endpoints included the incidence and event rates of hypoglycaemia during the 24-week on-treatment period, the active titration period (weeks 0–12), and the maintenance period (weeks 13-24).
- Documented symptomatic hypoglycaemia was defined as an event that was symptomatic with a confirmatory blood glucose reading (≤70 mg/dL or <54 mg/dL). Severe hypoglycemia was defined as an event requiring assistance from another person to administer carbohydrate, glucagon, or other resuscitative actions. Confirmed hypoglycaemia included documented symptomatic or asymptomatic hypoglycemia (≤70 mg/dL or <54 mg/dL) and severe events, if any. Hypoglycemia that occurred between 0000 h and 0559 h was defined as nocturnal. Other safety outcomes included body weight and adverse events (AEs). Change in basal insulin dose was also assessed, although this was not a pre-specified endpoint.

The complainant stated that he/she also looked at the study entry (NCT02738151) on clinicaltrials.gov where the only relevant pre-specified outcome mentioned was the secondary outcome measure 'Event rate of hypoglycaemia per ADA classification [Time Frame: Baseline to Week 24]'. There was no mention of hypoglycaemia rates during the 0-12 week period.

The complainant alleged that Sanofi produced misleading promotional material which placed undue emphasis on favourable results from a safety endpoint that was not a primary or secondary outcome and he/she was unclear whether it was a pre-specified endpoint. Furthermore, these data were obtained from 12 weeks of a 24-week study, with only brief mention of the overall results of the study.

When writing to Sanofi, the Authority asked it to consider the requirements of Clauses 7.2 and 7.3 of the Code.

RESPONSE

Sanofi submitted that the leavepiece in question was based on the BRIGHT study, the results of which were presented as three posters at the American Diabetes Association, June 2018. The BRIGHT study was the first head-to-head randomised controlled trial comparing the efficacy and safety of insulin glargine 300 units/mL and insulin degludec 100 units/mL in combination with oral anti-hyperglycaemic drugs with or without glucagon-like peptide-1 receptor agonists in 929 people with type 2 diabetes. The primary endpoint of the study was the change in HbA1c from baseline to week 24. Pre-specified safety endpoints included the incidence and event rates of hypoglycaemia during the 24-week on-treatment period, which consisted of the active titration period (weeks 0–12), and the maintenance period (weeks 13–24). Sanofi stressed it was important to note that this study used identical titration algorithms for the comparator insulin and a pre-stated objective of achieving appropriate titration within the defined 12-week titration period, meaning a comparison of this predefined period was valid and clinically relevant. A full publication of the study was also now available online.

Sanofi understood that the complainant alleged that the leavepiece was misleading as it placed undue emphasis on one of the safety endpoints. Sanofi disagreed with this assessment and submitted that it accurately reflected the BRIGHT study in a fair, unambiguous and scientifically balanced way and fulfilled all the requirements of the Code, both in letter and in spirit. Sanofi denied breaches of Clauses 7.2 and 7.3.

Sanofi explained that the folded leavepiece on its first page clearly stated the overall study objectives ie to compare efficacy and safety of the two insulins. The results of the primary endpoint of the study were also stated prominently on this page. Since the primary endpoint of the study was met, Sanofi did not consider it inappropriate or misleading to present secondary endpoint data, especially when they pertained to patient safety. The following page (the third page of the leavepiece when folded, and 'incorrectly' called the 'back page' by the complainant) contained four summary messages; the first reiterated the results of the primary endpoint and the second cited the results of two of the three safety endpoints that were comparable between the two products. The results of the remaining safety endpoint (which is the subject of the complaint) were cited in the third and fourth bullet points. Sanofi submitted that these results showed a difference between the two arms and were therefore covered in more detail inside the leavepiece and were clearly presented from the outset within the context of the primary endpoint and the overall safety results. The first page inside the leavepiece (when opened fully) included a visual presentation of important features of the study design, including inclusion criteria, target fasting plasma glucose (FPG) range and a statement on baseline demographics. The primary and safety endpoints were also clearly and prominently presented. Sanofi considered, in the context of a leavepiece, that this was

sufficient information displayed upfront on essential components of the study for the reader to understand its design and main endpoints. Sanofi appreciated that two inner pages of the folded leavepiece highlighted the hypoglycaemia results of the titration phase in a visual manner, however, it strongly believed that this was justifiable and allowable under the Code for several reasons:

1 The titration phase of the study (typically 0-12 weeks) was critical in any randomised clinical trial assessing the safety and efficacy of a basal insulin analogue. Patient's insulin was aggressively titrated in this period to achieve target FPG before the right dose could be determined and maintained for the remaining study period, ie maintenance phase (12-24 weeks). It could be argued that, particularly in this insulin naïve group of patients, any incidence of hypoglycaemia in this period could adversely affect the clinician's/patient's confidence with insulin therapy thereby preventing efficient titration of insulin to achieve desired FPG level as well as impacting patient adherence/compliance and motivation with therapy, eventually affecting overall management of diabetes. This critical phase and any potential incidence of hypoglycaemia carried even greater significance to clinicians in real world clinical practice of managing patients with type 2 diabetes. This was reflected in clinical guidelines eg the American Association of Clinical Endocrinologists (AACE) guidelines stated that 'minimising risk of hypoglycaemia is a priority'. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) guidelines stated 'Personalisation is necessary, balancing the benefits of glycaemic control with its potential risks, taking into account the adverse effects of glucose lowering medications (particularly hypoglycaemia)'. Sanofi submitted it was therefore absolutely relevant (as required by Clause 7.3) to discuss the titration phase results in this leavepiece.

2 Titration phase hypoglycaemia incidence and event rate was clearly a 'pre-specified' endpoint therefore it had made no attempt to highlight a result that was not stated as a pre-specified endpoint in the study. This was also discussed in the full publication.

3 Titration phase incidence and event rate of hypoglycaemia were 'safety' endpoints. Sanofi stated that it was important to appreciate that safety endpoints of hypoglycaemia in diabetes trials were of major clinical significance to prescribers along with HbA1c change. An episode of hypoglycaemia independent of the severity, frequency and time of the day could adversely affect a patient's condition both in the short-term and may also cause long-term complications. Sanofi considered that highlighting hypoglycaemia endpoints for discussion was essential with reference to the BRIGHT study.

4 Whilst the titration phase hypoglycaemia results were graphically presented, Sanofi submitted that it was important to emphasise here that the results of anytime and nocturnal hypoglycaemia in the maintenance and full study period were stated in clear bold statements on the same pages where titration phase results were presented. Sanofi stated that the overall study results and maintenance period results (where no difference between the two insulins were noted) had been stated as clear statements at three different places in the leavepiece. Sanofi submitted that it was also worth pointing out that these statements had been written in the same font size, font type and carried equal space as the statements on titration phase. Using the Forest plot was designed to show not just the result, but also the confidence intervals, which would give health professionals a greater depth of information of the results. The results for the titration phase safety endpoint had been shown in full, with some results crossing the unity line, further showing desire for full transparency. Sanofi stated that it should be appreciated that visual presentation was the most appropriate method to explain forest plots results with confidence intervals at various thresholds and there had been no attempt to visually over-emphasise the results. Moreover, Sanofi submitted that it was expected that any leavepiece was read altogether as one standalone item therefore, any discussion on the balance of one particular endpoint should be seen in the context of the full leavepiece not individual pages or sides.

5 The study reported the primary endpoint as showing non-inferiority in change in HbA1c for insulin glargine 300 units/mL vs insulin degludec 100 units/mL. Sanofi submitted that whilst titration phase, anytime hypoglycaemia incidence and event rate showed favourable results for Toujeo, all other secondary efficacy and safety endpoints reported similar results for the two comparator insulins therefore Sanofi did not consider that any attempt was made to selectively highlight or report results that benefitted Toujeo. Sanofi submitted that it had generated a fair and accurate leavepiece based on the study evidence where the only difference between the two insulins was showing a favourable result for Toujeo.

Based on these arguments, Sanofi stated it was confident that the leavepiece was not only factually accurate (as also acknowledged by the complainant) but it also clearly and fairly reflected the relevant and most important outcomes of the study. In Sanofi's opinion it was sufficiently complete to allow the reader to place appropriate weight to the results presented. Sanofi did not consider that the item was misleading or misrepresenting and therefore denied any breach of Clauses 7.2 and 7.3.

PANEL RULING

The Panel noted that the leavepiece solely discussed the BRIGHT study (Rosenstock *et al*, 2018). The front page of the leavepiece featured the BRIGHT study logo next to the title 'First head-to-head randomised controlled trial comparing the efficacy and safety of Toujeo vs. insulin degludec 100 units/

mL in insulin-naïve patients with Type 2 diabetes'. Below the heading it was stated that Toujeo showed comparable HbA1c reduction vs insulin degludec with lower incidence and event rates of anytime hypoglycaemia (≤3.9mmol/L and <3.0mmol/L) and lower event rates of nocturnal hypoglycaemia (≤3.9mmol/L) in the titration period, which was qualified with a footnote as being the period 0-12 weeks.

The Panel noted the parties' submissions about the two different orders in which the pages were likely to be read; the page identified as the back page by the complainant was considered by Sanofi to be the third page. There was no evidence before the Panel about the order in which recipients would read the leavepiece. Nonetheless, the Panel considered that although readers would likely see the outside back page when first opening the gate-folded leavepiece, a reasonable number would read the detail of the inside triple page spread first. That the outside back page in question summarised what might be described as the previous four pages, supported the Panel's view.

When opened, the first inside page gave a description of the primary endpoint (change in HbA1c from baseline to week 24) and the non-inferiority margin. Below this, two secondary endpoints were described: incidence and event rates of anytime confirmed hypoglycaemia and incidence and event rates of nocturnal confirmed hypoglycaemia, followed by a description of the study design, a multicentre, open-label, 24-week study. The Panel noted that these endpoints were listed in the study as pre-specified safety endpoints. The Panel noted that the secondary outcome measures on clinicaltrials.gov that the complainant referred to differed from those currently on the website.

The middle page of the inside triple page spread showed a graphical representation of the results for anytime confirmed hypoglycaemia during the titration period. Two forest plots of the titration period results (incidence and event rates per patient per year) for anytime confirmed hypoglycaemia (≤3.9mmol/L and <3.0mmol/L) along with related claims occupied most of the page, followed by two bullet points at the bottom of the page: the first bullet point highlighted the anytime hypoglycaemia (≤3.9mmol/L) titration period results in favour of Toujeo, and the final bullet point stated 'Comparable anytime hypoglycaemia incidence and event rates during the maintenance period and 24-week study period'. A similar layout was used on the third inside page with regard to the results for nocturnal confirmed hypoglycaemia, with the graphical representation of the titration period results with related claims occupying most of the page, followed by two bullet points at the bottom of the page: the first bullet point highlighted the nocturnal hypoglycaemia (≤3.9mmol/L) titration period results in favour of Toujeo, and the final bullet point stated 'Comparable nocturnal hypoglycaemia incidence and event rates during the maintenance period and 24-week study period'.

The page on the outside cover contained four summary statements: the first pertained to comparable and effective HbA1c reduction with Toujeo and insulin degludec 100 units/mL in insulin-naïve patients with type 2 diabetes at 24 weeks (primary endpoint); the second stated 'Comparable incidence and event rates of anytime and nocturnal hypoglycaemia in the maintenance and full 24-week study periods'; the third stated 'Lower anytime (24hr) confirmed hypoglycaemia during the titration period' and gave the relative percentage reduction for incidence and events (≤3.9mmol/L) in favour of Toujeo; the fourth statement stated 'Lower nocturnal (00.00-06.00hr) confirmed hypoglycaemic events during the titration period' and gave the relative percentage reduction for events (≤3.9mmol/L) in favour of Toujeo. Incidence and events rates for nocturnal confirmed hypoglycaemia during the titration period where the 95% confidence interval crossed 1 were not highlighted as text statements in the leavepiece. According to the study, the rate of confirmed nocturnal hypoglycaemia (<3.0mmol/L) was comparable with both treatments during the titration period. Further, the incidence of nocturnal confirmed hypoglycaemia (≤3.9mmol/L and <3.0mmol/L) was comparable with both treatments during the titration period; this was not highlighted on the front page, summary page or in the claims below the forest-plots.

The final page was the prescribing information for Toujeo.

The Panel noted that the BRIGHT study was a head-to-head 24-week study which demonstrated non-inferiority of Toujeo vs insulin degludec for the primary endpoint, which was HbA1c change from baseline to week 24. The Panel further noted that the safety endpoints, hypoglycaemia incidence and event rates (anytime and nocturnal) over 24 weeks, were comparable with both insulins.

The Panel noted Sanofi's submission that pre-specified safety endpoints included the incidence and event rates of hypoglycaemia during the 24-week on-treatment period, which consisted of the active titration period (weeks 0-12), and the maintenance period (weeks 13-24) and that the study used identical titration algorithms for both treatment arms. The Panel further noted Sanofi's justification that dedicating two pages of the leavepiece to the visual representation and description of the hypoglycaemia results from the titration period was relevant as that time-period (0-12 weeks) was critical when assessing the safety and efficacy of a basal insulin analogue. The Panel noted Sanofi's submission that since the primary endpoint of the study was met, it could not be considered inappropriate or misleading to present secondary endpoint data, especially when they pertained to patient safety.

The Panel noted the clinical relevance of the hypoglycaemia data during the titration period. The Panel considered that it was not unreasonable to present secondary endpoint data, nor was it unreasonable to present such data from the titration period, if it was presented in the context of the full

study period and with proportionate emphasis. The Panel acknowledged the bullet points referencing comparable hypoglycaemia incidence and event rates during the maintenance and 24-week study periods at the bottom of the middle and third inside pages and as the second bullet point on the summary back page. In the Panel's view, a single bullet point at the bottom of the middle and third inside pages was disproportionate to the prominent graphical representation of the titration period data which occupied most of those pages; insufficient weight had been given to the hypoglycaemia results for the full 24-week treatment period, which were comparable between the treatment arms. The Panel considered the immediate impression to a busy health professional; in the Panel's view, the titration period hypoglycaemia results were designed to be the primary take home message of the leavepiece and the final bullet points at the very bottom of the pages in question were wholly insufficient to qualify the immediate impression given. The Panel further noted that the secondary efficacy endpoint result, change in FPG from baseline to week 24, which showed a greater reduction with insulin degludec vs Toujeo, was not mentioned in the leavepiece at all and this appeared to the Panel not to be consistent with Sanofi's submission that all other secondary efficacy and safety endpoints reported similar results for the two insulins. The Panel disagreed with Sanofi's submission that it did not make any attempt to selectively highlight or report results that benefitted Toujeo. The leavepiece predominately highlighted the hypoglycaemia results during the 12-week titration period, which favoured Toujeo, without sufficient balance. The Panel disagreed with Sanofi's submission that it accurately reflected the BRIGHT study in a fair, unambiguous and scientifically balanced way and that it had fulfilled all the requirements of the Code. The Panel considered that the leavepiece placed disproportionate emphasis on the results that had favoured Sanofi's product and, in that regard, misrepresented the study and the immediate impression given by the second and third pages of the inside triple page spread was a misleading comparison of the two insulins. A breach of Clause 7.2 and 7.3 was ruled.

Complaint received **22 August 2018**

Case completed **17 October 2018**