CASE AUTH/2600/4/13

NOVO NORDISK v SANOFI

Promotion of Lyxumia

Novo Nordisk complained about claims in a leavepiece, mailer and on exhibition panels used by Sanofi to promote Lyxumia (lixisenatide). Lyxumia was a glucagon-like peptide-1 (GLP-1) receptor agonist for the treatment of type 2 diabetes. It was indicated in combination with oral glucose lowering medicines and/or basal insulin when these, together with diet and exercise, did not provide adequate glycaemic control. Novo Nordisk marketed Victoza (liraglutide) which was also a GLP-1 receptor agonist for use in type 2 diabetes.

The detailed response from Sanofi is given below.

With regard to the claim 'The only once-daily prandial GLP-1 receptor agonist' Novo Nordisk alleged that as all GLP-1 receptor agonists reduced elevated blood glucose levels, including post-prandial glucose (PPG), through a glucose dependent mode of action the claim was not justified or substantiated by the available scientific evidence.

Novo Nordisk alleged that Sanofi had introduced the term '*prandial* GLP-1 receptor agonist' (emphasis added) with no clinical grounds for differentiation within the GLP-1 receptor agonist class, in an attempt to differentiate Lyxumia from Victoza and mislead health professionals. The Victoza summary of product characteristics (SPC) summarised evidence showing that Victoza reduced PPG in all three meals of the day. The same conclusion was made by Kapitza *et al* (2013). Sanofi inferred that any differences in PPG efficacy between Lyxumia and Victoza arose from profound differences in their action; ie Lyxumia strongly inhibited gastric emptying whilst Victoza had a negligible effect. This conclusion was reached based on inconclusive evidence and rodent studies were cited for Victoza. Clinical studies showed Victoza significantly delayed gastric emptying, but these were not cited by Sanofi.

Novo Nordisk stated that for Lyxumia to reliably be labelled as a 'once-daily prandial' agent, it had to reduce absolute prandial glucose levels across all meals. The available evidence could not support the PPG lowering effect of Lyxumia throughout the whole day. Sanofi refused to provide data to allow Novo Nordisk to assess whether Lyxumia demonstrated this efficacy. Sanofi had provided modified data.

Novo Nordisk therefore alleged that the claim 'The only once-daily prandial GLP-1 receptor agonist' was misleading as it implied greater efficacy than supported by the evidence and it disparaged Victoza.

The Panel noted that health professionals would be familiar with the term 'prandial' in the claim that Lyxumia was 'The only once-daily prandial GLP-1 receptor agonist' but considered that GLP-1 receptor agonists were not commonly described as such. The Panel disagreed with Sanofi's submission that Lyxumia was widely described in the literature as a 'prandial GLP-1 receptor agonist'. The only paper submitted to describe Lyxumia in this way was Horowitz *et al* which was published in 2013; Sanofi had been involved in the production of the paper before it was peer reviewed. It was not stated whether the company had reviewed the paper. Given the authors' reference to the approval of Lyxumia by the European Medicines Agency in February 2013, the Panel queried whether the paper had been published before the mailer and the leavepiece had been approved (7 and 5 February respectively). In the Panel's view, health professionals would not be familiar with 'prandial' as a description of a GLP-1 receptor agonists. Other authors only described GLP-1 receptor agonists as short- or long-acting. Short-acting GLP-1 receptor agonists, eg Lyxumia, produced a modest reduction in fasting blood glucose levels and a strong reduction in post-prandial glucose levels. Conversely, long-acting GLP-1 receptor agonists, eg Victoza, produced a strong reduction in fasting blood glucose levels and a modest reduction in post-prandial glucose levels. Thus both short- and long-acting GLP-1 receptor agonists affected fasting and post-prandial blood glucose levels but each had a greater effect on one or the other.

The Panel noted that Lyxumia and Victoza were both once-daily medicines. Therefore the claim that Lyxumia was the only once-daily prandial GLP-1 receptor agonist implied that Victoza had no prandial action at all. The Panel accepted that in a 28 day study, Lyxumia had been shown to decrease post-prandial glucose levels. Although the after breakfast (standardised test meal) data showed an advantage for Lyxumia compared to Victoza nonetheless, Victoza decreased post-prandial glucose levels (Kapitza *et al*). The Panel further noted that Section 5.1 of the Victoza SPC stated that '[Victoza] has 24 hour duration of action and improves glycaemic control by lowering fasting and post-prandial blood glucose in patients with type 2 diabetes mellitus'. The Lyxumia SPC stated 'When administered once daily, [Lyxumia] improves glycaemic control through the immediate and sustained effects of lowering both post-prandial and fasting glucose concentrations in patients with type 2 diabetes'.

The Panel considered that as the claim stated that Lyxumia was the only once-daily prandial GLP-1 receptor agonist, it implied that the only other once-daily GLP-1 receptor agonist, ie Victoza, had no prandial effect at all which was not so. The Panel considered that readers would be unfamiliar with the term 'prandial GLP-1 receptor agonist'.

The claim was misleading and exaggerated and the Panel ruled breaches of the Code. The claim disparaged Victoza by implying that it had no prandial action and a further breach of the Code was ruled.

Upon appeal by Sanofi, the Appeal Board referred to Section 5.1, Pharmacodynamic properties, of the Lyxumia SPC and noted that under a heading of 'Mechanism of action' only the last sentence referred to what Sanofi had referred to as the predominant mechanism of action of Lyxumia; delay in gastric emptying.

The Appeal Board noted Sanofi's submission that prandial meant 'pertaining to a meal' and that Lyxumia fitted this description in at least two ways – ie its predominant mechanism of action and its requirement to be given once daily, within the hour prior to the first meal of the day or the evening meal. The Appeal Board noted that Lyxumia lowered both fasting and post-prandial glucose concentrations. Victoza also had a dual mechanism of action. It was given once daily at any time, independent of meals. The Appeal Board did not consider that the term 'prandial' in the claim 'The only once-daily prandial GLP-1 receptor agonist' could be used to distinguish Lyxumia from Victoza. 'Prandial' in the claim at issue appeared to have a different meaning compared with when it was currently more usually used to describe insulins or glucose regulators (glinides). In the Appeal Board's view, health professionals would not understand what Sanofi meant by a 'prandial GLP-1 receptor agonist'; such medicines were more usually, and currently, differentiated in the literature as long-acting (Victoza) or short-acting (Lyxumia). The Appeal Board considered that the claim that Lyxumia was 'The only once-daily prandial GLP-1 receptor agonist' was misleading and exaggerated. The Appeal Board upheld the Panel's rulings of breaches of the Code. The Appeal Board further considered that the claim disparaged Victoza as it implied that Victoza had no prandial action which was not so. The Appeal Board upheld the Panel's ruling of a breach of the Code. The appeal was thus unsuccessful.

Novo Nordisk alleged that the claim 'A positive addition can make all the difference' which appeared in the leavepiece and on the exhibition stand over-promised on the benefits that Lyxumia offered. No treatment could make all the difference and 'all' implied a greater improvement to a person with type 2 diabetes than simply a post-prandial glucose lowering effect over one meal in the day.

The Panel disagreed with Sanofi's submission that the claim related broadly to the treatment of diabetes and not directly to Lyxumia. The claim was an integral part of Lyxumia promotional material; it appeared adjacent to a picture of the Lyxumia pre-filled pen. 'Positive addition' was written in a font the same colour as the pen. In the Panel's view readers would associate the broad, unqualified claim with Lyxumia.

The Panel considered that as the claim was unqualified it was impossible to know what it meant with regard to Lyxumia treatment; readers would interpret it in their own way. In that regard the Panel considered that the claim was misleading and exaggerated; breaches of the Code were ruled.

With regard to the claim 'Strong evidence supporting the use of Lyxumia as add-on to basal insulin', Novo Nordisk alleged that results from the cited references, Rosenstock *et al* (2012) and Riddle *et al* (2012), were insufficient to support the use of 'strong' and that the European Medicines Agency (EMA) appeared to hold a similar opinion.

The Panel noted that Lyxumia was indicated as adjunctive therapy and in that regard Sanofi would have had to submit evidence to the regulatory authorities that such use of Lyxumia was well tolerated and effective. The Panel considered that to describe such evidence as 'strong' implied some special merit – all evidence provided for the grant of any marketing authorization had to be robust. In that regard the Panel considered that the claim exaggerated the strength of the data and it ruled a breach of the Code.

Novo Nordisk Limited complained about the promotion of Lyxumia (lixisenatide) by Sanofi.

Lyxumia was a glucagon-like peptide-1 (GLP-1) receptor agonist for the treatment of type 2 diabetes. It was indicated in combination with oral glucose lowering medicines and/or basal insulin when these, together with diet and exercise, did not provide adequate glycaemic control. Novo Nordisk marketed Victoza (liraglutide) which was also a GLP-1 receptor agonist for use in type 2 diabetes.

The material at issue was a representatives' leavepiece (ref GBIE.LYX.13.01.14 (PRO 20055)); a one-off mailer (ref GBIE.LYX.13.02.02 (PRO 20140)) sent in February to inform health professionals about the availability of Lyxumia and to offer the opportunity for further product information and exhibition panels used at the Diabetes UK Annual Professional Conference, 13-15 March 2013. The leavepiece was withdrawn from use on 13 May 2013.

1 Claim 'The only once-daily prandial GLP-1 receptor agonist'

This claim appeared in the leavepiece, the mailer and on the exhibition stand.

COMPLAINT

Novo Nordisk stated that Victoza and Lyxumia were both once-daily GLP-1 receptor agonists. All GLP-1 receptor agonists effectively reduced elevated blood glucose levels, including post-prandial glucose (PPG), through a glucose dependent mode of action. Novo Nordisk alleged that the claim at issue was not justified or substantiated by the available scientific evidence.

Novo Nordisk alleged that Sanofi had introduced the term '*prandial* GLP-1 receptor agonist' (emphasis added) with no clinical grounds for differentiation within the GLP-1 receptor agonist class, in an

attempt to differentiate Lyxumia from Victoza and mislead health professionals.

The Victoza summary of product characteristics (SPC) summarised evidence to show Victoza effectively reduced PPG in all three meals of the day. The same conclusion was made by Kapitza *et al* (2013).

With regard to gastric emptying of Victoza and Lyxumia, Sanofi inferred that any differences in PPG efficacy between the two medicines arose from profound differences in their action; ie Lyxumia exerted a strong inhibition of gastric emptying, whilst Victoza exerted a negligible effect on gastric emptying. This conclusion was reached based on inconclusive evidence and rodent studies were cited for Victoza. Existing human studies showed Victoza significantly delayed gastric emptying, but these were not cited by Sanofi.

Novo Nordisk believed that for Lyxumia to reliably be labelled as a 'once-daily prandial' agent, it was necessary for it to reduce absolute prandial glucose levels across all meals in the day. Novo Nordisk alleged that the available evidence could not support the PPG lowering effect of Lyxumia throughout the whole day. Sanofi refused to provide data requested by Novo Nordisk in order to assess whether Lyxumia demonstrated this efficacy. Sanofi had provided modified data.

Novo Nordisk therefore alleged that the claim 'The only once-daily prandial GLP-1 receptor agonist' was misleading as it implied greater efficacy than supported in the evidence and disparaged Victoza. Breach of Clauses 7.2, 7.10 and 8.1 were alleged.

RESPONSE

Sanofi noted that GLP-1 receptor agonists were used in the treatment of type 2 diabetes and activated the endogenous GLP-1 receptor. Once activated, this receptor acted on multiple pathways to enhance the action of endogenous insulin, regulated endogenous glucagon secretion and delayed gastric emptying. These factors all served to reduce circulating glucose concentrations and improve the hyperglycaemia that was characteristic of diabetes. Lyxumia and Victoza were the only once-daily GLP-1 receptor agonists licensed for use in the UK (the other GLP-1 receptor agonists were used twice daily or once weekly).

The degree to which each pathway was activated had been shown to depend upon the pharmacodynamic profile of the individual agents. The reference to 'prandial' was made to distinguish Lyxumia from Victoza on the basis that a clear distinction was seen between the two in terms of their mode of action which reflected different pharmacokinetic profiles and pharmacodynamic effects. This was clearly reported in the scientific literature, and confirmed by different requirements for posology for the products. There was a specific requirement for Lyxumia to be given at meal times, as would be expected for a prandial agent; this was captured in Section 4.2 of the Lyxumia SPC. No such requirement existed for Victoza which was to be given 'at any time, independent of meals' as per Section 4.2 of its SPC.

Sanofi noted that Novo Nordisk had: challenged the definition of 'prandial'; purported that Victoza had a prandial effect and that Lyxumia could not therefore be termed 'the only once-daily prandial' agent; stated that Victoza had an effect on gastric emptying and contended that Lyxumia failed to maintain a prandial effect throughout the entire day.

Sanofi submitted that Novo Nordisk had not put forward sufficient evidence to support its allegations. Sanofi was confident that the information presented was a balanced and accurate representation of the up-to-date evidence base, and that the materials at issue complied with the Code.

Sanofi submitted that the treatment of diabetes needed to be considered to understand the term 'prandial' within context. One of the common methods of treating long-standing type 2 diabetes was to administer basal (long-acting) insulin, which met the background need for insulin matched to the body's own production of glucose, which happened at a constant rate. Basal insulin, with a constant level of activity, could stabilise the background blood glucose levels during periods of fasting, but could not control the peak in blood glucose that occurred with meals. Other prandial agents, such as fast-acting or prandial insulin, were administered in conjunction with meals and were required to account for these post-prandial peaks. Lyxumia ultimately had the same effect as prandial insulin – it accounted for the peaks in blood glucose that occurred after meals and was licensed for the treatment of type 2 diabetes.

Contrary to Novo Nordisk's statement, Sanofi had not introduced the term 'prandial' to describe Lyxumia. The term prandial was already well known – a 'prandial insulin' was to be taken with a meal and reduced the post-prandial blood glucose peak. Clear clinical grounds existed that already saw GLP-1 receptor agonists categorised as 'prandial' – given with meals to affect the post-prandial blood glucose related to a meal, or 'non-prandial' – given irrespective of meals to affect primarily the fasting blood glucose levels. Lyxumia was widely described as a 'prandial' GLP-1 receptor agonist in peer reviewed scientific literature. Sanofi submitted that describing Lyxumia in this way was a fair representation of current scientific understanding.

Meier (2012) summarised existing knowledge and made a clear distinction between two modes of action of GLP-1 receptor agonists based on the predominant effect:

- Short-acting GLP-1 receptor agonists (such as exenatide and Lyxumia) predominantly lower post-prandial glucose levels and insulin concentrations via retardation of gastric emptying. (This resulted in a reduced rate of glucose release from the stomach and a direct reduction on the rise in glucose related to meals).
- Long-acting GLP-1 receptor agonists (such as exenatide LAR (long-acting release) and Victoza) predominantly lowered fasting blood glucose levels through stimulation of insulin secretion and reduction of glucagon levels.

Marathe *et al* (2013) described the relationship between gastric emptying, post-prandial glycaemia and incretin hormones. The authors summarised the current understanding that some GLP-1 receptor agonists 'slow gastric emptying and that [this effect] is, at least in some cases, an important mechanism by which they lower post-prandial glucose excursions'. Further, that due to differing half-lives GLP-1 receptor agonists 'vary in the magnitude of their effects on pre- versus post-prandial glycaemia'.

Marathe *et al* compared the two GLP-1 receptor agonists with a relatively short duration of action (Lyxumia and exenatide) with those of a longer duration of action (Victoza and exenatide LAR). They highlighted the observations from studies of type 2 diabetics that the short-acting agents – exenatide and Lyxumia – acted by lowering post-prandial glucose excursion through a predominant effect of sustained inhibition of gastric emptying. Conversely, the longer-acting medicines – exenatide LAR and Victoza – acted to lower fasting (pre-prandial) glucose levels through a predominant effect on the insulin/glucagon hormonal axes. The authors concluded that the short-acting agents – Lyxumia included – had a prolonged effect on post-prandial hyperglycaemia that was not demonstrated with the long-acting agents (including Victoza). The authors clearly differentiated the two categories of GLP-1 receptor agonists.

Fineman *et al* (2012) similarly reviewed the clinical effects of the GLP-1 receptor agonists and made the same distinction between the two groups, based on pharmacokinetic exposure – intermittent (from short-acting GLP-1 receptor agonists) and continuous (from long-acting receptor agonists). The authors made the same conclusions as Marathe *et al*, in that there were two distinct classes of GLP-1 receptor agonists: those which predominantly affected post-prandial glucose reduction, and those which predominantly affected fasting blood glucose.

Horowitz *et al* (2013) reviewed the clinical evidence available for Lyxumia and recognised its relatively short half-life and short duration of action, its once-daily regimen, as well as its clinical effect primarily mediated through lowering the exaggerated post-prandial glucose excursion in type 2 diabetes. The authors concluded it to be a 'once-daily prandial GLP-1 receptor agonist'.

To summarise, this wide body of evidence consistently classified GLP-1 receptor agonists as prandial or non-prandial agents:

- Prandial GLP-1 receptor agonists had a shorter half-life. They strongly inhibited gastric emptying and prevented a post-prandial increase in blood glucose (ie after food). Lyxumia and fast-acting exenatide (which was, however, administered twice a day) acted in this way.
- Non-prandial GLP-1 receptor agonists had a longer half-life. Long-acting GLP-1 receptor agonists had a self-limiting inhibitive effect on gastric emptying and food resorption. Non-prandial GLP-1 receptor agonists (such as Victoza) primarily affected fasting blood glucose levels.

Further to the scientific observation and supporting the 'prandial' description of Lyxumia was the specific requirement that it be administered at meal times, as would be expected with any other prandial agent, for example a prandial insulin. This was in direct contrast to the requirements for Victoza; the SPC indicated that it could be administered at any time of the day and specifically stated that this needed to be independent of meal times. This explicitly acknowledged a fundamental difference between the two medicines – Lyxumia was 'prandial' both in mechanism of action and the requirements for meal time administration, Victoza was neither.

Sanofi submitted that to describe Lyxumia as a 'prandial' agent was therefore entirely in keeping with the available evidence and Novo Nordisk had not provided any argument as to why this reference should not be cited to substantiate Lyxumia as a 'prandial' GLP-1 receptor agonist. Sanofi used 'prandial' quite rightly to differentiate Lyxumia from Victoza but this was not in an attempt to mislead – it correctly reflected the current understanding of the GLP-1 receptor agonist class of medicines, and was intended to meet the required standards of the Code.

Novo Nordisk stated that the Victoza SPC and Kapitza *et al* both indicated that Victoza effectively reduced post-prandial glucose throughout the day. Whilst on the surface this was a factually correct statement, on deeper examination it was clear to Sanofi that this would not be sufficient to support an implied claim that Victoza was a 'prandial' GLP-1 receptor agonist (and thereby to invalidate the observation that Lyxumia was the only once-daily prandial GLP-1 receptor agonist).

The 'prandial' description of Lyxumia was based on the observations conclusively outlined above: that its predominant effect on glycaemic control was through a reduction in post-prandial glucose excursion – that was the rise in blood glucose above the fasting/baseline level that occurred after eating. This was in contrast to the action of Victoza which acted predominantly to reduce fasting glucose levels.

Kapitza *et al* compared the pharmacodynamics of Lyxumia and Victoza and examined the impact of 28 days' treatment with each agent in type 2 diabetics. The study primarily assessed the ability of each medicine to suppress the prandial glucose excursion that followed a standardised test meal. The study demonstrated that after 28 days' treatment with Lyxumia, the post-meal excursion of glucose above baseline levels was more than completely abolished, whereas with Victoza, a significant glucose excursion remained and a highly significant difference was confirmed between the two medicines (reduction in glucose excursion: -129% vs -41% respectively, $p<0.0001$). The authors also demonstrated that Victoza had a significantly greater effect than Lyxumia in lowering fasting glucose levels, consistent with the different clinical attributes of these medicines.

Sanofi noted that Novo Nordisk maintained that the authors concluded that Victoza effectively reduced PPG. However, early in the discussion the authors stated that '… the PPG-lowering effects observed

with some GLP-1 receptor agonists (lixisenatide and exenatide, but not liraglutide) appear to be due primarily to slowing of gastric emptying' which supported a true difference between the two medicines. Although a small reduction in glucose excursion was reported with Victoza, it was acknowledged as not being the result of the predominant mode of action of Victoza. This was clearly insufficient to substantiate a claim that Victoza was a prandial GLP-1 receptor agonist in the same way that had been demonstrated for Lyxumia.

Furthermore, it was clear from the supporting evidence provided by Novo Nordisk as part of the inter-company dialogue, that rather than acting on post-prandial glucose excursions, the effect of Victoza was to reduce fasting/baseline blood glucose. Data provided by Novo Nordisk clearly demonstrated a reduction in fasting blood glucose levels of 2-3mmol/L in each of three different studies (0.7-2.4mmol/L in the SPC).

As a consequence of this decreased baseline blood glucose level, there was also a decrease in post-prandial glucose levels of the same magnitude (the SPC quoted 1.7-2.7mmol/L). It was clear that this post-prandial reduction was mediated through the reduction in the fasting glucose levels rather than through any specific reduction in post-prandial glucose excursion – the post-prandial reduction seen simply reflected a lowered baseline, not the reduction in post-prandial excursion as seen with Lyxumia (4.5-8.0mmol/L post-prandial fall, on a background of minimal change in baseline levels of 0.4-1.2mmol/L).

In conclusion, although this observation supported the wording in the Victoza SPC that both fasting and post-prandial hyperglycaemia were reduced, this wording could not be extended so far as to support a claim that Victoza was also a prandial agent. To do so would be akin to recognising that a basal insulin which reduced baseline/fasting blood glucose levels (such as insulin determir or insulin glargine) could also be called a prandial agent – and Sanofi was sure that neither party would ever countenance such a suggestion.

As already discussed, the effect of Victoza on delaying gastric emptying was recognised as being only of minor impact and not the prominent mechanism through which it exerted a glucose lowering effect – the effects on the insulin/glucagon axis in lowering fasting plasma glucose was the predominant mode of action. This was in contrast to the effects of Lyxumia which acted predominantly to delay gastric emptying and abolish the post-prandial glucose excursion. This was important as the different methods of action were the main features that distinguished the medicines.

Novo Nordisk alleged that inconclusive evidence was cited when referring to the effects of Victoza on gastric emptying. This was an unexpected statement given that Sanofi had cited the Victoza SPC which stated 'the mechanism of blood glucose lowering also involves a minor delay in gastric emptying'. Beyond this observation, it was clear that this observation was substantiated by studies in humans – the evidence cannot be claimed 'inconclusive':

- Juhl *et al* (2002) compared a single dose of Victoza with placebo in patients with type 2 diabetes and described only a 9% reduction/15 minute delay in gastric emptying.
- Degn *et al* (2004) performed a similar study and at the end of one week's treatment there was no detectable difference in the rate of gastric emptying between patients receiving Victoza and placebo, either at breakfast or at the evening meal.
- Flint *et al* (2011) performed a three week comparison between Victoza (0.6, 1.2 and 1.8mg/day) and placebo in patients with type 2 diabetes. Although no significant reduction in gastric emptying was seen in the lower and higher doses, a small but statistically significant reduction was seen with the middle dose. The authors, however, commented that their study was of too short a duration for the expected tolerance to the gastric emptying to have developed to allow the study to assess this parameter appropriately and thus questioned the relevance of this result.

In summary, the current balance of scientific information indicated that the gastric emptying effect of Victoza appeared to be a minor component of its mechanism of action, and one which was not sustained. Tolerance developed rapidly (within days to weeks) and this was clearly relevant to treating a long-term condition.

Sanofi submitted that with Novo Nordisk's suggestion that for Sanofi to claim that Lyxumia was a prandial agent, it should demonstrate a lowering PPG level consistently throughout the day had no basis in science nor precedent – the fact that Lyxumia abolished the meal time glucose excursion defined its prandial mechanism of action, not the number of meals that this remained effective for after a dose was given. This effect did not need to be equally marked after all meals, or even to persist for all three meals in a day after a single dose. Novo Nordisk would agree that prandial insulin, for example, was likely to be effective only for the meal in relation to which it was administered.

That stated, however, Sanofi had provided evidence during inter-company dialogue to support the fact that there was significant reduction in the post-meal glucose excursion after each of three meals in the day after a morning dose of Lyxumia. To substantiate the fact did not require 'the full data analysis' referred to by Novo Nordisk. Furthermore, Lorenz *et al* (2012) showed that compared with placebo, the reduction in post-prandial exposure to glucose was significantly reduced by Lyxumia, given once in the morning, after three standardised test meals throughout the day (breakfast, lunch, dinner).

In summary, the prevailing scientific opinion and evidence classed GLP-1 receptor agonists as prandial or non-prandial according to their dominant mode of action. Lyxumia had a post-prandial action and was clearly classed as a prandial GLP-1 receptor agonist; Victoza clearly had a fasting mechanism of action and was classed as a non-prandial GLP-1

receptor agonist. Beyond this, a direct comparison by randomised clinical trial had demonstrated that Lyxumia completely abolished the post-prandial glucose excursion after a test meal, demonstrating a highly significant advantage over Victoza which had only a minor impact on the same parameter. Furthermore, randomised clinical trials showed that the post-prandial effect of Lyxumia was maintained throughout the day.

Sanofi thus denied a breach of Clauses 7.2, 7.10 and 8.1.

PANEL RULING

The Panel noted that the claim at issue was that Lyxumia was 'The only once-daily prandial GLP-1 receptor agonist'. The Panel noted that health professionals would be familiar with the term 'prandial' but considered that GLP-1 receptor agonists were not commonly described as such. The Panel disagreed with Sanofi's submission that Lyxumia was widely described in the literature as a 'prandial GLP-1 receptor agonist'. The only paper submitted by the parties to describe Lyxumia in this way was Horowitz *et al* which was published in 2013. Under 'Acknowledgements' at the end of the paper it was stated that Sanofi had been involved in the production of the paper and had had the opportunity to review the paper for scientific accuracy before the paper was peer reviewed. It was not stated whether the company had reviewed the paper. The authors cited the approval of Lyxumia by the European Medicines Agency in February 2013 and so in that regard the Panel queried whether the paper had been published before the mailer and the leavepiece had been approved (7 and 5 February respectively). In the Panel's view, health professionals would not be familiar with the description of a GLP-1 receptor agonist as a 'prandial GLP-1 receptor agonist'.

The Panel noted that apart from Horowitz *et al*, authors only described GLP-1 receptor agonists as short- or long-acting agents. Short-acting GLP-1 receptor agonists, eg Lyxumia, produced a modest reduction in fasting blood glucose levels and a strong reduction in post-prandial glucose levels. Conversely, long-acting GLP-1 receptor agonists, eg Victoza, produced a strong reduction in fasting blood glucose levels and a modest reduction in post-prandial glucose levels. Thus both short- and long-acting GLP-1 receptor agonists affected fasting and post-prandial blood glucose levels but each had a greater effect on one or the other.

The Panel noted that Lyxumia and Victoza were both once-daily medicines. Therefore the claim that Lyxumia was the only once-daily prandial GLP-1 receptor agonist implied that Victoza had no prandial action at all. The Panel accepted that in a 28 day study, Lyxumia had been shown to decrease post-prandial glucose levels. Although the after breakfast (standardised test meal) data showed an advantage for Lyxumia compared to Victoza nonetheless, Victoza did decrease post-prandial glucose levels from those which were seen at baseline (Kapitza *et al*). The Panel further noted that in Section 5.1 of the Victoza SPC it was stated that '[Victoza] has 24 hour duration of action and improves glycaemic control by lowering fasting and post-prandial blood glucose in patients with type 2 diabetes mellitus'. The comparable statement in the Lyxumia SPC read 'When administered once daily, [Lyxumia] improves glycaemic control through the immediate and sustained effects of lowering both post-prandial and fasting glucose concentrations in patients with type 2 diabetes'.

The Panel noted that Sanofi had submitted that there was not enough data to support a claim that Victoza was a prandial agent. In the Panel's view however, this was not the issue; the claim at issue was about what Lyxumia was and by implication, what Victoza was not. The Panel considered that as the claim stated that Lyxumia was the only once-daily prandial GLP-1 receptor agonist it implied that the only other once-daily GLP-1 receptor agonist ie Victoza had no prandial effect at all which was not so. The Panel considered that readers would be unfamiliar with the term 'prandial GLP-1 receptor agonist'. The Panel considered that the claim was misleading and exaggerated and ruled a breach of Clause 7.2 and 7.10. The Panel further considered that the claim disparaged Victoza by implying that it had no prandial action. A breach of Clause 8.1 was ruled. These rulings were appealed by Sanofi.

APPEAL FROM SANOFI

Sanofi submitted that the Panel had recognised that clear differences existed between the two once-daily GLP-1 receptor agonists – ie that Lyxumia was a short-acting agent and Victoza a long-acting agent, and that the different durations of action directly related to the presence/absence (respectively) of an important effect on gastric emptying after a meal.

Sanofi submitted that 'prandial' had been used to describe the short-acting GLP-1 agonists reflecting this mechanism of action. The Panel however ruled that this claim was inappropriate on the basis that: 'prandial' was not widely applied to describe GLP-1 agonists; health professionals would be unfamiliar with the term, and Victoza also reduced post-prandial glucose and Lyxumia could not, therefore, be the only prandial GLP-1 agonist.

Sanofi submitted that short-acting GLP-1 receptor agonists had been described as 'prandial' in the literature since at least 2010. Further references were provided to demonstrate the description of 'prandial exenatide' and Lyxumia as a 'prandial GLP-1' (Elkinson and Keating 2013, Pinkney *et al* 2013). Sanofi further submitted that 'prandial' was by definition 'related to meals' and this term would be readily understood, especially by health practitioners who cared for people with diabetes. It was widely used to describe both the increased blood glucose levels related to meals, and as a descriptor for medicine classes – prandial glucose regulators ('glinides') and prandial (rapid-acting) insulins in particular – each taken at meal times to control the exaggerated post-prandial glucose excursion in type 2 diabetes. To conclude that health professionals would not recognise the term 'prandial GLP-1 receptor agonist' failed to appreciate the knowledge and experience of those to whom the material was directed.

Sanofi noted that the Panel acknowledged that Lyxumia was a short-acting agent and Victoza a long-acting agent, and that the different durations of action directly related to the presence or absence, respectively, of the important effect of delayed gastric emptying after a meal. The presence (or absence) of this meal-time effect conveyed the different pattern of blood glucose control that was seen with each agent – ie the predominant effect of Lyxumia to reduce the post-prandial glucose excursion and that of Victoza to reduce fasting (or baseline) blood glucose levels.

Sanofi submitted that the Panel identified a statement within the Victoza SPC that Victoza reduced post-prandial glucose, but had incorrectly assumed that this equated to a specific prandial ('meal-related') effect. The Panel had failed to appreciate that reducing absolute post-prandial glucose levels was different to the specific prandial effect of abolishing or significantly reducing the post-meal increase – the 'glucose excursion' – above baseline levels. A reduction in absolute post-prandial glucose levels could be achieved in the absence of any specific prandial effect through the reduction in baseline (pre-meal) glucose levels alone. An identical increase in post-meal blood glucose, but on the background of a lowered baseline, resulted in a reduced post-prandial glucose value, despite the size of the post-meal increase being unchanged. A reduced prandial glucose excursion required a meaningful reduction in the rise of post-meal glucose levels relative to pre-meal values, as was seen with Lyxumia. Kapitza *et al* showed that Lyxumia completely abolished the post-prandial glucose excursion and was significantly different to Victoza in this respect; this confirmed the unique prandial action of Lyxumia and justified the description of 'the only once-daily prandial GLP-1'.

Sanofi further submitted that 'prandial' could be applied to the posology of Lyxumia. It was the only once-daily GLP-1 agonist required to be given at meal times – the SPC directed 'within the hour prior to the first meal of the day or the evening meal'. Conversely, the SPC for Victoza indicated that it was 'administered once daily at any time, independent of meals'. This was a clear point of differentiation and in itself justified the description 'only once-daily prandial GLP-1 agonist'. In summary, Sanofi submitted that in light of the evidence currently available the description of Lyxumia as 'the only once-daily prandial GLP-1 agonist' was not misleading or exaggerated, and by implication did not disparage Victoza.

COMMENTS FROM NOVO NORDISK

Novo Nordisk stated that a health professional's interpretation of the word 'prandial' was the key consideration.

Sanofi appropriately stated that 'prandial' by definition related to meals and correctly linked the health professional's understanding of the word prandial with the individual's experience of using prandial glucose regulators ('glinides') and prandial rapid-acting insulins. Glinides stimulated pancreatic beta cells to produce more insulin in a glucose independent manner, while rapid-acting insulin served as simple replacement for inadequate insulin secretion during periods of high blood glucose concentration – eg 'prandial periods'. Therefore every health professional would know that both classes of medicine worked in a rapid-acting, glucose independent manner. These agents covered the period immediately after the dose and needed to be administered before every main meal in order to provide full daily prandial coverage. This was also reflected in the SPCs for medicines in these two classes.

Novo Nordisk therefore agreed with Sanofi that this was exactly the understanding (linked to use of glinides and rapid-acting insulins) a health professional would have when presented with the terms 'prandial' and 'basal'.

Novo Nordisk noted that in contrast, GLP-1 receptor agonists worked in a glucose dependent manner, at periods when blood glucose concentration was high (eg in prandial periods after meals), to stimulate pancreatic beta cells to produce more insulin. This had been confirmed by the low rate of hypoglycaemia in clinical trials for medicines in this class. Therefore all GLP-1 receptor agonists including long-acting agents had a prandial effect as supported by the scientific evidence and reflected in the Victoza and once weekly exenatide (Bydureon) SPCs. Novo Nordisk was not aware of any original scientific research to prove the opposite nor had Sanofi provided this evidence.

The Panel correctly noted that apart from Horowitz *et al*, the authors of the other three publications submitted by Sanofi only described GLP-1 receptor agonists as short- or long-acting. Of the two references provided by Sanofi with its appeal, Novo Nordisk noted that Elkinson and Keating was a very recently published R&D insight report. The publication was authored by employees from the Adis R&D Insight database, who described the database as being 'An exhaustive compilation of drug programs worldwide, with drug profiles updated daily using information from company contacts, press releases, international conferences, company websites, and medical journals'. Consequently the report was subject to bias towards Sanofi. Novo Nordisk noted that Pinkney *et al*, used the word 'prandial' just once in the abstract to describe the dosing of exenatide twice daily ie in relation to meals, rather than Sanofi's interpretation that the word 'prandial' described the comparative effects of either treatment of reducing post-prandial glucose. The authors neither suggested a lack of post-prandial glucose control with Victoza nor made a distinction between the two products based on post-prandial glucose lowering efficacy.

As a result of the above, Novo Nordisk alleged that these two publications did not provide convincing evidence that prandial could be widely applied to describe GLP-1 receptor agonists. Novo Nordisk thus agreed with the Panel that health professionals would be unfamiliar with the term 'prandial GLP-1 receptor agonist'.

Novo Nordisk noted that as provided in inter-company dialogue, the scientific evidence showed that Victoza lowered post-prandial glucose over all three meals of the day. Therefore, Novo Nordisk alleged that health professionals could only conclude from the scientific evidence that Victoza had some prandial action. The same applied to Bydureon (Kim *et al* 2007). Making the distinction within the GLP-1 receptor agonist class based on the word 'prandial' was misleading, as all agents acted with a prandial effect due to their mechanism of action.

Novo Nordisk stated that in Kapitza *et al*, which compared the post-prandial glucose lowering effect of short- and long-acting GLP-1 receptor agonists after the first meal post-injection, the short-acting agent was expected to provide better efficacy over this first meal period. As correctly noted by the Panel this did not mean that a long-acting compound (Victoza) showed no prandial effect at all after breakfast. Additionally, Novo Nordisk alleged that the claim 'The only once-daily prandial GLP-1 receptor agonist' implied post-prandial glucose efficacy across 24 hours. Kapitza *et al* concluded that Victoza provided better post-prandial glucose control than Lyxumia beyond the morning meal. Novo Nordisk was disappointed with the lack of transparency and proper scientific dialogue from Sanofi with regard to the refusal to share the data from Kapitza *et al* needed to establish medicine profiles beyond the morning meal.

In inter-company dialogue Sanofi presented an analysis of the post-prandial glucose excursions dividing the post-prandial period into the prior fasting plasma glucose level and the additional increment of glucose as a specific 'prandial glucose excursions'. Novo Nordisk alleged that this had no grounding in clinical practice whereby post-prandial glucose was measured as an absolute level.

Novo Nordisk emphasised that fasting blood glucose concentration was an important aspect in the management of a patient's blood glucose profile, and should not be eliminated from any analysis of the data. Novo Nordisk alleged that the improved fasting blood glucose lowering efficacy of Victoza vs Lyxumia was the consequence of a longer half-life as recognised by Kapitza *et al*, and not caused by any mechanism of action specific to Victoza as a 'non-prandial' agent. Any glucose level above 7mmol/l was recognised as abnormally raised blood glucose, a sign of diabetes. Therefore the glucose dependent reductions in plasma glucose seen with Victoza in Kapitza *et al*, were clinically relevant to both the post-prandial and fasting plasma glucose periods. Graphical manipulations of the post-meal data vs baseline, served no other purpose than to disparage the efficacy of Victoza. Novo Nordisk noted that if the same graphical manipulation was applied to the 24 hour blood glucose profile for Lyxumia, it might be concluded that Lyxumia increased the blood glucose levels after the second meal post-injection (lunch). Novo Nordisk believed that Sanofi would strongly object to this conclusion.

In addition, Novo Nordisk alleged that it was clear from Kapitza *et al* that Victoza also decreased prandial glucose 'excursions' – unfortunately Kapitza *et al*, failed to report whether Victoza decreased prandial glucose 'excursions' from baseline level. In addition, Novo Nordisk was further disappointed that Sanofi presented prandial glucose 'excursions' discussions to the Panel but failed to mention Flint *et al* who clearly demonstrated that Victoza significantly decreased post-prandial glucose 'excursions'.

Novo Nordisk agreed with the Panel that the claim in question implied that Victoza had no prandial effects at all, which was incorrect.

Novo Nordisk alleged that Sanofi had attempted to introduce an artificial distinction in the GLP-1 receptor agonist class by categorising them into 'prandial' and basal (similar to insulin). As suggested by Sanofi, Victoza reduced baseline blood glucose levels and not 'prandial' blood glucose levels as defined by health professionals' experience with glinides and rapid-acting insulin.

It appeared that Sanofi had compared the action of Victoza to long-acting (basal) insulins which provided support during the post-absorptive state and covered 'basal' insulin needs. Novo Nordisk reiterated that Victoza reacted differently to basal insulin and specifically acted during periods of high blood glucose, especially during post-prandial periods.

Novo Nordisk disagreed with Sanofi's statement that the Panel had acknowledged the difference between short- and long-acting GLP- receptor agonists and that the different durations of action related to the presence or absence of gastric emptying. In its ruling, the Panel stated that it recognised the different pharmacokinetic profiles of the two products, but did not relate this to the presence or absence of gastric emptying to support the duration of effect. Any assertion of an 'absence' of a gastric emptying effect in relation to Victoza was factually incorrect – various clinical studies and the Victoza SPC described an effect of Victoza on gastric emptying. Novo Nordisk emphasised that the effect of Lyxumia on gastric emptying had been studied just in the first meal post-injection and there was no indication of what the effect would be to subsequent meals during the day.

Nevertheless, Novo Nordisk stated that slowing of gastric emptying was just one of the less well explored potential mechanisms of action attributed to GLP-1 receptor agonists that might play a small role in the overall efficacy of all of them.

Novo Nordisk alleged that this argument was based on inconclusive and unfounded evidence and should not be used as a basis to make a misleading claim.

Novo Nordisk noted that in its appeal, Sanofi used another potential definition of the word 'prandial' in relation to its required dosage at meal times. This definition was very different to its previous definition: 'prandial had been used as the descriptive term for the short-acting-GLP-1 agonists reflecting this mechanism of action'. This showed that Sanofi had exploited the word 'prandial' and used it in an ambiguous way in order to make a misleading

claim. Nevertheless, even if the time of medicine administration was considered, Victoza in this context might still be considered as 'prandial' as it could be given at any time, including meal times.

Based on the above, Novo Nordisk supported the Panel's rulings of a breach of Clauses 7.2, 7.10 and 8.1 of the Code.

APPEAL BOARD RULING

The Appeal Board referred to Section 5.1, Pharmacodynamic properties, of the Lyxumia SPC and noted that under a heading of 'Mechanism of action' it was stated that:

> 'Lixisenatide is a selective GLP-1 receptor agonist. The GLP-1 receptor is the target for native GLP-1, an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from the pancreatic beta cells.
>
> Lixisenatide action is mediated via a specific interaction with GLP-1 receptors, leading to an increase in intracellular cyclic adenosine monophosphate (cAMP). Lixisenatide stimulates insulin secretion when blood glucose is increased but not at normoglycaemia, which limits the risk of hypoglycaemia. In parallel, glucagon secretion is suppressed. In case of hypoglycaemia, the rescue mechanism of glucagon secretion is preserved.
>
> Lixisenatide slows gastric emptying thereby reducing the rate at which meal-derived glucose appears in the circulation.'

The Appeal Board thus noted that only the last sentence referred to what Sanofi had referred to as the predominant mechanism of action of Lyxumia; delay in gastric emptying.

The Appeal Board noted Sanofi's submission that prandial meant 'pertaining to a meal' and that Lyxumia fitted this description in at least two ways – ie its predominant mechanism of action and its requirement to be given once daily, within the hour prior to either the first meal of the day or the evening meal. The Appeal Board noted that Lyxumia lowered both fasting and post-prandial glucose concentrations. Victoza also had a dual mechanism of action. It was given once daily at any time, independent of meals. The Appeal Board did not consider that the term 'prandial' in the claim 'The only once-daily prandial GLP-1 receptor agonist' could be used to distinguish Lyxumia from Victoza. 'Prandial' in the claim at issue appeared to have a different meaning compared with when it was currently more usually used to describe insulins or glucose regulators (glinides). In the Appeal Board's view, health professionals would thus not understand what Sanofi meant by a 'prandial GLP-1 receptor agonist'. The Appeal Board noted that GLP-1 receptor agonists were more usually, and currently, differentiated in the literature according to length of action ie long-acting (Victoza) and short-acting (Lyxumia). The Appeal Board considered that the claim that Lyxumia was 'The only once-daily prandial GLP-1 receptor agonist' was misleading and exaggerated. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.10. The Appeal Board further considered that the claim disparaged Victoza as it implied that Victoza had no prandial action which was not so. The Appeal Board upheld the Panel's ruling of a breach of Clause 8.1. The appeal was thus unsuccessful.

2 Claim 'A positive addition can make all the difference'

This claim appeared in the leavepiece and on the exhibition stand.

COMPLAINT

Novo Nordisk alleged that the claim over-promised on the benefits that Lyxumia offered. No treatment could make all the difference and 'all' implied a greater improvement to a person with type 2 diabetes than simply a post-prandial glucose lowering effect over one meal in the day. Breaches of Clauses 7.2 and 7.10 were alleged.

RESPONSE

Sanofi submitted that this claim was simple, clear and unambiguous, did not imply any benefit beyond that of adding any additional anti-hyperglycaemic agent at the point at which additional therapy was required, and above all did not imply that Lyxumia (or any medicine) would deliver any particular effect – only that there was the potential for benefit to occur. It was a stimulus to the reader to consider additional therapy for patients with type 2 diabetes when this was needed. To direct that choice towards Lyxumia as being the sought-after positive addition was the intent of the rest of the item, not this individual claim.

Sanofi submitted that the claim related broadly to the treatment of diabetes and not directly to Lyxumia (although Sanofi recognised, of course, that it was promotional material for Lyxumia). The claim did not refer to any expected effect, positive or negative. Critically, if that was the implication, the use of the conditional 'can' (as opposed to the direct 'will' or 'does') made it clear that not every patient would be so affected. Taking all these factors into consideration, Sanofi did not consider that the claim was misleading or all-embracing.

Sanofi noted that Novo Nordisk had alleged that the claim attempted to portray an all-encompassing effect of Lyxumia and referred to benefits beyond glycaemic control. Sanofi failed to see how this could be so. There was no reference to or even suggestion of any benefit to 'blood pressure, lipid control, neuropathy and other complications', and to suggest such an association was at odds with the nature of the item.

Sanofi concluded that the claim was clear, unambiguous and invited readers to consider that when additional therapy was required for patients with type 2 diabetes, additional therapy should be considered. Sanofi expected that the typical reader

would reach this same conclusion, and failed to see how any other interpretation would be arrived at. Sanofi denied a breach of Clauses 7.2 or 7.10.

PANEL RULING

The Panel disagreed with Sanofi's submission that the claim 'A positive addition can make all the difference' related broadly to the treatment of diabetes and not directly to Lyxumia. The claim was an integral part of Lyxumia promotional material; it appeared adjacent to a picture of the Lyxumia pre-filled pen. 'Positive addition' was written in a font the same colour as the pen. In the Panel's view readers would associate the broad, unqualified claim with Lyxumia.

The Panel considered that as the claim was unqualified it was impossible to know what it meant with regard to Lyxumia treatment; readers would interpret it in their own way. In that regard the Panel considered that the claim was misleading and a breach of Clause 7.2 was ruled. The Panel further considered that the broad claim was exaggerated and a breach of Clause 7.10 was ruled.

3 Claim 'Strong evidence supporting the use of Lyxumia as add-on to basal insulin'

This claim appeared in the leavepiece, the mailer and on the exhibition stand and was referenced to Rosenstock *et al* (2012) and Riddle *et al* (2012).

COMPLAINT

Novo Nordisk stated that while both Rosenstock *et al* and Riddle *et al* were designed to be of sufficient quality, the published results of each randomised clinical trial demonstrated insubstantial efficacy to support the claim 'strong'. Novo Nordisk noted that the European Medicines Agency (EMA) appeared to hold a similar opinion on this point, as mentioned by Sanofi in its letter of 3 April 2013. Novo Nordisk alleged a breach of Clause 7.10.

RESPONSE

Sanofi submitted that it had claimed 'Strong evidence to support benefit', not 'Evidence of strong benefit'.

To provide an overview of the evidence that supported the use of Lyxumia with basal insulin, Sanofi conducted three randomised controlled trials in this clinical setting (GetGoal-L, GetGoal-L Asia, GetGoal-Duo1) each adequately powered and with a sufficient number of patients to draw a meaningful conclusion. This programme provided the greatest Phase III trial reported experience of a GLP-1 receptor agonist used in combination with basal insulin. In itself, one well conducted, randomised trial took a high position in any ranking of evidence (second only to systematic review in the Oxford CBEM Level of Evidence scale). It was difficult to consider three well-conducted randomized clinical trials showing similar results as anything but strong.

Although Novo Nordisk continued to make its point over the strength of the evidence, the EMA had clearly recognised that this was adequate to support a licensed indication for the use of Lyxumia in combination with basal insulin.

Sanofi submitted that the evidence base for Lyxumia in combination with basal insulin was sufficiently robust to be considered 'strong'; further, the evidence itself was of sufficient strength to support the granting of a relevant marketing authorization to allow its use in this way. Sanofi was confident that this was reflected in the nature of the marketing authorization. The company denied a breach of Clause 7.10.

PANEL RULING

The Panel noted that Lyxumia was indicated for the treatment of type 2 diabetes to achieve glycaemic control in combination with an existing treatment regimen that included insulin, where the existing medicinal therapy, together with exercise and diet, had failed to provide adequate glycaemic control. In that regard the Panel noted that the company would have had to submit evidence to the regulatory authorities that such use of Lyxumia was well tolerated and effective. The Panel considered that to describe such evidence as 'strong' implied some special merit – all evidence provided for the grant of any marketing authorization had to be robust. In that regard the Panel considered that the claim exaggerated the strength of the data and it ruled a breach of Clause 7.10.

Complaint received **29 April 2013**

Case completed **7 August 2013**