CASE AUTH/3202/6/19

PHARMACIST v NAPP

Alleged off-licence promotion of Invokana

An anonymous and non-contactable individual, who described him/herself as a concerned pharmacist, complained about the promotion of Invokana (canagliflozin) by Napp at a national conference of a diabetes society. Invokana was indicated for the treatment of adults with insufficiently controlled type 2 diabetes as an adjunct to diet and exercise as monotherapy and in combination.

The complainant alleged that the representative on Napp's exhibition stand explained the new renal outcome data and how Invokana could be the first in therapy for slowing the progression of chronic kidney disease in type 2 diabetes. The representative put forward a valid argument to use Invokana in this patient group but on inspection of the summary of product characteristics (SPC), this was an off-licence indication and under the Code should not have been advocated.

The detailed response from Napp is given below.

The Panel noted that Section 4.1 of the Invokana SPC cross-referred to study results in relation to, *inter alia*, effects on glycaemic control and cardiovascular events in later sections of the SPC.

The Panel noted that when using a product for its licensed indication there might be other beneficial outcomes for which the product was not licensed. It was not unacceptable to refer to such benefits so long as they were placed clearly within the context of the licenced indication for the product which was the primary reason to prescribe. Napp accepted that renal outcomes were not a licensed indication but described them as an additional benefit.

According to Napp, the representative in question was clear that he/she had presented the CANVAS-R data on renal benefits in line with the SPC and he/she had not answered any questions outside of the licence, referring such questions to the medical team.

The Panel noted that the CANVAS programme was an integrated analysis of two similarly designed trials, CANVAS and CANVAS-R, to assess CV safety and efficacy of Invokana versus placebo in Type 2 diabetics who were at risk of cardiovascular disease. Pre-specified hypotheses testing of secondary outcomes was discontinued as the first secondary outcome hypothesis failed to demonstrate statistical significance. Consequently, all secondary outcomes underwent exploratory analyses and the associated hypothesis tests were not performed. The Panel did not have a copy of either study but noted that the Napp Diabetes Training Hub Module 3 – The Canvas Programme stated that exploratory analyses of renal endpoints suggest that Invokana may reduce the risk of renal events (the progression of albuminuria and the composite renal endpoint

of a 40% reduction in eGFR, renal replacement therapy or renal death). P values were not calculated for these exploratory outcomes. Napp stated that the SPC did not refer to the analyses of renal events from the integrated CANVAS programme but did refer to data from the individual CANVAS-R trial in relation to reduction in the progression of albuminuria and reducing the decline of eGFR versus placebo. The Panel noted Napp's detailed submissions about the Canvas-R data and CREDENCE trials. The Panel noted Napp's submission that the secondary renal outcomes component to the CANVAS programme demonstrated, *inter alia*, a significant 47% relative risk reduction for the time to the first adjudicated nephropathy event.

The subsequent CREDENCE trial specifically addressed potential renal protection in type 2 diabetes and was stopped early for clinical efficacy. The Panel did not have a copy of this study. Napp submitted that representatives had been briefed and trained in detail that they could not promote CREDENCE results. The Panel noted a section of the Credence briefing made it clear that when attending third party meetings at an exhibition stand any questions about Credence should be referred to a local MSL or medical information. The section 'What renal information can be used currently' advised representatives that they could talk about renal outcomes from CANVAS-R using the sales aid, and when discussing this information to note the disclaimer 'Improved renal outcomes with Invokana are an additional benefit only and not a licensed indication'. It was also made clear that some patients in Credence were off-licence in that they had eGFR below 60mL/min/1.73m2 and that representatives could not talk reactively or proactively about patients outside of the licence. If asked about CREDENCE, reactive responses were given including that representatives could state that CREDENCE was stopped early for efficacy reasons, and that representatives could not proactively talk about the CREDENCE study, or engage in discussions about the study results or the nature of what these might mean, or encourage health professional discussions that 'lead' on CREDENCE. In the Panel's view, following the briefing about reactive responses might solicit questions about the study results. Representatives were advised to pass requests to medical information or an MSL.

In addition, the Panel noted that the briefing for the meeting in question advised that, if asked a medical question, a medical information request form 'can be completed' and that, in addition, a member of the medical team would also be available and should be able to speak to the health professional. Medical question was not defined and yet it appeared to the Panel that the evidence from both parties was that what might be described as medical matters were discussed. The briefing also stated that if asked a question outside of licence the health professional should be put in contact with one of the medical affairs team.

Whilst the complainant did not refer to the sales aid Napp stated that it would have been used at the stand. The Panel noted that whilst it had some concerns about the sales aid, the Renal section featured a banner at the top of each page which read 'Improvements in renal outcomes with Invokana are additional benefits and not licensed indications'.

The Panel noted that an Invokana leavepiece which, according to Napp, was available from the stand on a page entitled 'Glucose-Lowering medication in type 2 diabetes: Overall Approach' included a summary of the ADA/EASD guidelines and stated that 'Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOT's and recommended Invokana or other SGLT2i with evidence of

reducing HF and/or CKD progression in CVOT if eGFR was adequate. The following page entitled 'Why do the new guidelines favour SGLT2is over DPP4is and SUs?' included a table showing that Invokana had a positive impact across a number of categories including CKD progression.

The Panel noted that another document available on the stand was entitled 'Practice Nurse – Beyond Glycaemic Control' and referred to the CREDENCE trial in a section headed Canagliflozin and renal benefits which described the trial and stated that it had been ended ahead of schedule following positive results suggesting that in future, drugs for diabetes control may also be selected on the basis of proven renal benefits.

The Panel noted that the conference included a Napp sponsored symposium entitled 'Diabetes and the cardio/renal axis: life changing practice in type 2 diabetes'. The Panel did not know whether the complainant had attended the symposium. Nonetheless, given the symposium and the foreseeable general professional interest in the renal data and the information available on the stand described above, it was not unsurprising that discussion about renal data occurred at the stand. The Panel did not know precisely what occurred including what was said by either party and how the discussion was initiated and there was no way of contacting the complainant for further information. In such circumstances, it was not possible to determine where the truth lay. The complainant bore the burden of proof and had not established, on the balance of probabilities, what was said and whether that discussion promoted Invokana for an unlicensed indication. There was no evidence that the representative had failed to maintain a high standard of ethical conduct in relation to the discussion at the exhibition stand. No breaches of the Code included Clause 2 were ruled.

In relation to the briefing materials, the Panel noted that it was important to be clear in briefing and training materials that in the CANVAS programme the secondary renal results were exploratory and p values had not been calculated. This was especially important given the emphasis attached to renal benefits in the sales materials. The Panel considered that the Diabetes Training Hub Module – The Canvas Programme, on balance, made the status of the secondary renal outcomes clear and in this regard ruled no breach of the Code.

In relation to training on the CREDENCE results, the Panel was concerned that a presentation did not make it clear how the results sat with the licensed indication, including that a sub population of patients sat outside the licensed indication. Nor was it made clear that the training was for educational purposes and did not reflect Napp's submission that the field force could not proactively talk about CREDENCE. The Panel was particularly concerned about the final page of the presentation which, in its view, bore the appearance of promotional material. It featured a prominent red triangle, divided horizontally into thirds, each third featured a promotional claim in prominent green font. The top third of the triangle read '30% Reduction in Death or Dialysis'. A horizontal red arrow adjacent to the claim led to a prominent claim in black font within an irregular yellow star which read 'FIRST AND ONLY SGLT2i with renal outcome data'. The strap line at the bottom of each slide read 'Credence to move medicine forward'. The Panel considered that the failure to include the appropriate caveats throughout in relation to the renal data and that the concluding slide contained strong promotional claims about renal outcome data meant that it advocated a course of action that was

likely to lead to a breach of the Code. A breach of the code was ruled. This ruling was upheld on appeal by Napp.

The Panel ruled a breach of the Code as it considered that high standards had not been maintained in relation to the briefing material. This ruling was upheld on appeal by Napp. The Panel considered that its concerns about the briefing material were adequately covered and decided to rule no breach of Clause 2 which was reserved to indicate particular censure.

An anonymous and non-contactable individual, who described him/herself as a concerned pharmacist, complained about the promotion of Invokana (canagliflozin) by Napp Pharmaceuticals Limited at a national conference of a diabetes society. Invokana was indicated for the treatment of adults with insufficiently controlled type 2 diabetes as an adjunct to diet and exercise.

COMPLAINT

The complainant alleged that the representative on Napp's exhibition stand explained the new renal outcome data and how Invokana could be the first in therapy for slowing the progression of chronic kidney disease in type 2 diabetes. The representative put forward a valid argument to use Invokana in this patient group but on inspection of the summary of product characteristics (SPC), this was an off-licence indication and under the Code should not have been advocated. The complainant stated that although he/she appreciated advances in healthcare he/she would prefer companies to stick to their licensed indications.

When writing to Napp, the Authority asked it to consider the requirements of Clauses 2, 3.2, 9.1, 15.2 and 15.9 of the Code.

RESPONSE

Napp stated that it promoted Invokana in the UK on behalf of Janssen Pharmaceuticals, which was the marketing authorization holder. Canagliflozin inhibited the sodium glucose co-transporter-2 (SGLT-2) in the proximal convoluted tubule of the kidney. SGLT-2 inhibition by canagliflozin resulted in 77-119g/day of urinary glucose excretion and it thus lowered blood glucose which was an important target in the pharmacological treatment of type 2 diabetes.

Canagliflozin was first licensed in November 2013 for glycaemic control in type 2 diabetes in addition to diet and exercise. The extensive clinical trial programme for canagliflozin indicated potential additional patient outcome benefits through SGLT-2 inhibition in atherosclerotic cardiovascular and chronic renal disease, commonly associated, life-shortening complications of type 2 diabetes. A regulatory requirement for all new medicines for type 2 diabetes was to demonstrate cardiovascular safety in a 'standardised' design, cardiovascular outcomes trial (CVOT). The CVOT for canagliflozin was the CANagliflozin cardioVascular Assessment Study – the CANVAS Programme. This event-driven trial demonstrated both cardiovascular safety and additional benefit by reduction in the composite primary endpoint for Major Adverse Cardiovascular Events (3-point MACE: non- fatal heart attack, non-fatal stroke and cardiovascular death), as well as reduction of hospitalisation for heart failure.

There was also a secondary renal outcomes component to the CANVAS Programme (called CANVAS-R) which demonstrated a significant 47% relative risk reduction for the time to the first

adjudicated nephropathy event (doubling of serum creatinine, need for renal replacement therapy, and renal death), the HR was 0.53 (95% CI: 0.33, 0.84) for canagliflozin (0.15 events per 100 patient-years) vs placebo (0.28 events per 100 patient-years). In addition, canagliflozin reduced progression of albuminuria 25.8% vs placebo 29.2% (HR: 0.73; 95% CI: 0.67, 0.79) in patients with baseline normo- or micro-albuminuria.

The CANVAS Programme results led the European Medicines Agency (EMA) to grant a licence extension in Europe in September 2018 to include the positive cardiovascular and renal outcomes (section 5.1 of the Invokana SPC). In recognition that 'both improvement in glycaemic control and reduction of cardiovascular morbidity and mortality are an integral part of the treatment of type 2 diabetes' the licenced indication changed from 'glycaemic control' to: 'the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise'. Section 5.1 of the SPC was updated to include the results of the CANVAS programme cardiovascular outcomes and the CANVAS-R renal outcomes. These aspects were incorporated into the representatives' education and promotional materials.

Because of the positive CANVAS trial, as well as the positive published CVOT (called the EMPA-REG trial) for Boehringer Ingelheim's Jardiance (empagliflozin), in October 2018 the American Diabetes Association/European Association for the Study of Diabetes updated their consensus treatment guidelines statement (Davies *et al* 2018). The consensus statement recommended the use of those SGLT2is with proven cardiovascular disease benefit in the treatment pathway for type 2 diabetics with established atherosclerotic cardiovascular disease or with evidence of reducing heart failure and/or chronic kidney disease progression in CVOTs with adequate eGFR. The SGLT-2is that fulfilled those criteria and that were named in the consensus guideline were empagliflozin and canagliflozin.

The improvements in renal outcomes were additional benefits, and not licensed indications because they were exploratory secondary outcomes of the CANVAS Programme. An additional large trial of Invokana was conducted to specifically address potential renal protection in type 2 diabetes with significant concomitant chronic kidney disease – the Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial. The trial was stopped early for clinical efficacy and was published in April 2019. The representatives had been briefed and trained in detail that they could not promote the CREDENCE results data. It was stated in the briefing document (ref UK/INV-19097) that 'It is important when discussing this information to note the disclaimer, "Improved renal outcomes with Invokana are an additional benefit only and not a licensed indication"'.

Napp noted that it had trained its sales force on the medical science and results from CANVAS and CREDENCE. Training on CREDENCE was for educational purposes only because there was an important and distinctly different mechanism of action for renal protection through sodium effects as part of SGLT2 inhibition. The effect was not via glycaemic control. Napp refuted a breach of Clause 15.9 as it had provided representatives with certified detailed briefing material on the technical aspects of Invokana including the fact that they could not proactively talk about the CREDENCE study.

Napp provided copies of the materials available to representatives at the one-day conference in question. Napp noted that the complainant could have attended any or all of the educational sessions including Napp's sponsored 45-minute educational and promotional symposium, 'Diabetes and the cardio/renal axis; changing practice in type 2 diabetes' which was part of the main agenda for all attendees.

Napp noted that there was only one employee, of the four who attended the conference, present on the promotional stand. The representative had been interviewed and he/she was clear that he/she presented the CANVAS-R data on renal benefits in line with the Invokana licence indication and SPC. As per the conference briefing, the representative was also clear that he/she could not answer any questions that could be outside of licence, referring such questions instead to the medical team.

Napp explained that representatives had been trained to use the interactive iPad sales aid (ref UK/INV-18038(2)) depending on what questions a health professional at the stand asked. Representatives did not simply take the health professional through the detail aid starting from page 1. In that regard, there were no page numbers but instead there were tabs at the right side of the pages to group the data into themes, eg renal benefits (2 pages), renal mechanism of action (2 pages), glycaemic control (4 pages), unmet need (2 pages), CV events etc. The complainant stated that he/she attended the Napp exhibition stand, but he/she had not provided any information as to what question(s) he/she might have asked the representative. Napp assumed that the complainant was interested in the CANVAS-R renal outcomes data, and if so, he/she would have been first taken through the most relevant pages of the detail aid. As part of their training in the use of the sales aid, representatives started on the pages that were most relevant to the health professional's question and highlighted important information at the top of the page (not as a footnote) before progressing to explain the data and/or graphs on the remainder of the page(s). By doing so, representatives made the licensed indication clear. When discussing the two renal benefits data pages the representative highlighted the statement at the top of the page, 'Improvements in renal outcomes with Invokana are additional benefits only and not licensed indications'. The data on those pages was also not inconsistent with the CANVAS renal outcomes data in Section 5.1 of the Invokana SPC.

Importantly, representatives had been briefed to make it clear that they could not respond to questions outside of licence for Invokana. They had been trained and briefed to pass on any off-licence questions to the medical affairs team. A medical information request form or a contact request form could be completed and someone from the medical team would contact the health professional. The representative who was on the Napp stand confirmed that he/she had followed his/her briefing and training and Napp therefore refuted a breach of Clause 3.2.

Napp submitted that its sales force had received face-to-face and online training, including briefing on organising speaker meetings, use of promotional materials and claims that must be within the Invokana current licensed indication. As Napp had emphasised that representatives must, at all times, maintain a high standard of ethical conduct in the discharge of their duties and must comply with all relevant requirements of the Code, it refuted a breach of Clause 15.2.

In summary, Napp stated that it had provided a comprehensive account of its involvement in the conference in question; it had explained how it had maintained high standards (Clause 9.1) and why it refuted breaches of Clauses 3.2, 15.2 and 15.9. The conduct of its representative had not brought discredit upon, or reduced confidence in, the pharmaceutical industry, and so Napp firmly believed it had upheld the highest standards as per Clause 2.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. The introduction to the Constitution and Procedure for the Prescription Medicines Code of Practice Authority

stated that anonymous complaints would be accepted but that, like all other complaints, the complainant had the burden of proving his/her complaint on the balance of probabilities. All complaints were judged on the evidence provided by the parties. The Panel noted that the parties' accounts differed; the complainant had provided no evidence to support his/her allegations and could not be contacted for more information.

The Panel noted that Invokana was indicated for the treatment of adults with insufficiently controlled type 2 diabetes as an adjunct to diet and exercise as monotherapy and in combination. Section 4.1 of the SPC also cross-referred to study results in relation to, *inter alia*, effects on glycaemic control and cardiovascular events in later sections of the SPC.

The Panel noted that when using a product for its licensed indication there might be other beneficial outcomes for which the product was not licensed. It was not unacceptable to refer to such benefits so long as they were placed clearly within the context of the licenced indication for the product which was the primary reason to prescribe. Napp accepted that renal outcomes were not a licensed indication but described them as an additional benefit.

The Panel noted the complainant's allegation that the representative explained new renal outcome data and how Invokana could be the first in therapy for slowing progression of chronic kidney disease in type 2 diabetes which, in the complainant's view, was an off-licence indication and should not be advocated.

According to Napp, the representative in question was clear that he/she had presented the CANVAS-R data on renal benefits in line with the SPC. The representative was also clear that he/she had not answered any questions outside of the product's licence, referring such questions to the medical team.

The Panel noted that the CANVAS programme was an integrated analysis of two similarly designed trials, CANVAS and CANVAS-R, to assess CV safety and efficacy of Invokana versus placebo in Type 2 diabetics who were at risk of cardiovascular disease. Pre-specified hypotheses testing of secondary outcomes was discontinued as the first secondary outcome hypothesis failed to demonstrate statistical significance. Consequently, all secondary outcomes underwent exploratory analyses and the associated hypothesis tests were not performed. The Panel did not have a copy of either study but noted that the Napp Diabetes Training Hub Module 3 – The Canvas Programme (UK/DIA-18032f) stated that exploratory analyses of renal endpoints suggest that Invokana may reduce the risk of renal events (the progression of albuminuria and the composite renal endpoint of a 40% reduction in eGFR, renal replacement therapy or renal death). P values were not calculated for these exploratory outcomes. Napp stated that the SPC did not refer to the analyses of renal events from the integrated CANVAS programme but did refer to data from the individual CANVAS-R trial in relation to reduction in the progression of albuminuria and reducing the decline of eGFR versus placebo. The Panel noted Napp's detailed submissions about the Canvas-R data and CREDENCE trials. The Panel noted Napp's submission that the secondary renal outcomes component to the Canvas programme demonstrated, *inter alia*, a significant 47% relative risk reduction for the time to the first adjudicated nephropathy event.

The Panel noted that the subsequent CREDENCE trial specifically addressed potential renal protection in type 2 diabetes and was stopped early for clinical efficacy. The Panel did not have before it a copy of this study. The Panel noted Napp's submission that representatives had been briefed and trained in detail that they could not promote CREDENCE results. The Panel

noted the Practical Guidance section of the Credence briefing, entitled 'Invokana Communication' (UK/INV-19097) made it clear that when attending third party meetings at an exhibition stand any questions about Credence should be referred to a local MSL or medical information. The section 'What renal information can be used currently' advised representatives that they could talk about renal outcomes from CANVAS-R using the sales aid, and when discussing this information to note the disclaimer 'Improved renal outcomes with Invokana are an additional benefit **only** and not a licensed indication'. It was also made clear that some patients in Credence were off-licence in that they had eGFR below 60mL/min/1.73m2 and that representatives could not talk reactively or proactively about patients outside of the licence. If asked about CREDENCE, reactive responses were given including that representatives could state that CREDENCE was stopped early for efficacy reasons, and it was stated that representatives could not proactively talk about the CREDENCE study, or engage in discussions about the study results or the nature of what these might mean, or encourage health professional discussions that 'lead' on CREDENCE. In the Panel's view, following the briefing about reactive responses might solicit questions about the study results. The account manager was advised to pass requests to medical information or an MSL.

In addition, the Panel noted that the staff briefing for the meeting in question (UK/INV-19047c) advised that, if asked a medical question, a medical information request form 'can be completed' and that, in addition, a member of the medical team would also be available on site and should be able to speak to the health professional. Medical question was not defined and yet it appeared to the Panel that the evidence from both parties was that what might be described as medical matters were discussed. The staff briefing also stated that if asked a question outside of licence the health professional should be put in contact with one of the medical affairs team.

Whilst the complainant did not refer to the sales aid (ref UK/INV-18038(2), Napp stated that it would have been used at the stand. In this regard, the Panel noted that whilst it had some concerns about the sales aid, the Renal section featured a banner at the top of each page which read 'Improvements in renal outcomes with Invokana are additional benefits and not licensed indications'.

The Panel noted that an Invokana leavepiece (ref UK/INV-18091(2)) which, according to Napp, was available from the stand on a page entitled 'Glucose-Lowering medication in type 2 diabetes: Overall Approach' included a summary of the ADA/EASD guidelines and stated that 'Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOT's and recommended Invokana or other SGLT2i with evidence of reducing HF and/or CKD progression in CVOT if eGFR was adequate. The following page entitled 'Why do the new guidelines favour SGLT2is over DPP4is and SUs?' included a table showing that Invokana had a positive impact across a number of categories including CKD progression.

The Panel noted that another document available on the stand was entitled 'Practice Nurse – Beyond Glycaemic Control (ref NA-INV-18200(1))' and referred to the CREDENCE trial in a section headed Canagliflozin and renal benefits which described the trial and stated that it had been ended ahead of schedule following positive results suggesting that in future, drugs for diabetes control may also be selected on the basis of proven renal benefits.

The Panel noted that the conference included a Napp sponsored symposium entitled 'Diabetes and the cardio/renal axis: life changing practice in type 2 diabetes'. The Panel did not know whether the complainant had attended the symposium. Nonetheless, given the symposium and

the foreseeable general professional interest in the renal data and the information within the material available on the stand described above, it was not unsurprising that discussion about renal data occurred at the stand. This was not unacceptable so long as such discussions complied with the Code as set out above. The Panel did not know precisely what occurred including what was said by either party and how the discussion was initiated and there was no way of contacting the complainant for further information. In such circumstances, it was not possible to determine where the truth lay. The complainant bore the burden of proof and had not established, on the balance of probabilities, what was said and whether that discussion promoted Invokana for an unlicensed indication. No breach of Clause 3.2 was ruled. Similarly, there was no evidence that the representative had failed to maintain a high standard of ethical conduct in relation to the discussion at the exhibition stand. No breach of Clause 15.2 was ruled. Noting its rulings above, the Panel also ruled no breach of Clause 2.

In relation to the complainant's concerns that an off-licence indication should not be advocated, the Panel examined the briefing materials. The Panel noted that it was important to be clear in briefing and training materials that in the CANVAS programme the secondary renal results were exploratory and p values had not been calculated. This was especially important given the emphasis attached to renal benefits in the sales materials. The Panel considered that the Diabetes Training Hub Module – The Canvas Programme, on balance, made the status of the secondary renal outcomes clear and in this regard ruled no breach of Clause 15.9.

In relation to training on the CREDENCE results, the Panel was concerned that a presentation entitled 'Credence Results (UK/INV-19124)' did not make it clear how the results sat with the licensed indication, including that a sub population of patients sat outside the licensed indication. Nor was it made clear that the training was for educational purposes and did not reflect Napp's submission that the field force could not proactively talk about CREDENCE. The Panel was particularly concerned about the final page of the presentation which, in its view, bore the appearance of promotional material. It featured a prominent red triangle, divided horizontally into thirds, each third featured a promotional claim in prominent green font. The top third of the triangle read '30% Reduction in Death or Dialysis'. A horizontal red arrow adjacent to the claim led to a prominent claim in black font within an irregular yellow star which read 'FIRST AND ONLY SGLT2i with renal outcome data'. The strap line at the bottom of each slide read 'Credence to move medicine forward'. The Panel considered that the failure to include the appropriate caveats throughout in relation to the renal data and that the concluding slide contained strong promotional claims about renal outcome data meant that it advocated a course of action that was likely to lead to a breach of the Code. A breach of Clause 15.9 was ruled. This ruling was appealed by Napp.

The Panel noted its comments and ruling of a breach of Clause 15.9 above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled in relation to the briefing material. This ruling was appealed by Napp. The Panel noted its concerns about the briefing material set out above and considered that these concerns were adequately covered by its ruling of a breach of Clause 9.1 and decided to rule no breach of Clause 2 which was reserved to indicate particular censure.

* * * * *

APPEAL BY NAPP

Napp appealed the Panel's ruling of breaches of Clauses 15.9 and 9.1. Napp submitted that as relevant background information, it was important to understand that the reason this educational presentation (UK/INV-19124) was delivered was not to provide the salesforce with this data to encourage them to promote it, but to explain the recently reported CREDENCE study design and data as and why there was such a great interest in the media and amongst health professionals. Most important was to explain why they were not allowed to talk about it. They were provided training and a briefing to pass on any reactive requests on CREDENCE from health professionals to the medical team.

Napp submitted that the presentation was delivered at a Napp one day off-site internal training day which was 'themed' around an explanation to the sales force of diabetic kidney disease, the CREDENCE trial design and recently published results (results published in April 2019). There was also refresher training and comparisons of the renal results within the CANVAS trial (published in 2017).

Napp submitted that a more detailed explanation of the presentation and sales force training were summarised below. The presentation entitled 'CREDENCE Results!' was provided in Napp's response to the complaint with six further training materials. This included mandatory online training modules completed by the salesforce prior to the internal training day. .

Napp submitted that the 38-slide presentation was educational training presented by two Napp medical affairs staff at an internal sales force and company personnel training day . The first opening slide of the presentation made it clear in bold red text that this was 'FOR INTERNAL USE ONLY'.

Napp submitted that the third slide highlighted in the centre a large bold '! WARNING – CONSIDER YOURSELF WARNED' on an orange background, and the speakers verbalised that the data being presented was for internal use only and not to be used or shared externally by the sales force. This was also made clear for slide 3 in the notes section of the job summary page in Zinc accompanying the certification of the job bag:

> 'Notes: Please note the purpose of slide 3 is to support a strict verbal briefing that none of this information is to be shared externally at this time.'

Napp therefore respectfully disagreed with the Panel's ruling that 'Nor was it made clear that the training was for educational purposes and did not reflect Napp's submission that the field force could not proactively talk about CREDENCE'. Slide 3 contained three warning sign motifs, which appeared sequentially as a slide build, and were used as visual cues to accompany the following three verbatim messages (see below). This information was delivered slowly and with a great deal of emphasis and explanation:

1 **CAUTION sign:** This sign supported the verbal instruction that the study was not within the product licence and must not be discussed with customers under any circumstances. The explanation given here was that Napp was providing the information for educational purposes ONLY.

2 **CCTV in operation sign:** This was used to support the point that Napp managers and Compliance were monitoring them and any inappropriate sharing of this data

with health professionals would result in a breach of the Code and disciplinary action.

3 **! WARNING - CONSIDER YOURSELF WARNED sign:** This sign appeared last in the build and was used to conclude the compliance discussion about the data. Therefore, if you do choose to discuss this with customers, there would be severe consequences.

In addition, Napp submitted that the detailed sales force briefing document (UK/INV-19097) was certified and sent to the sales force in April 2019, ahead of the training day where the slides (UK/INV-19124) were presented. This briefing was also referred to during the presentation on the training day, that representatives could not proactively talk about the CREDENCE study, nor engage in discussions about the study results or the nature of what these might mean or encourage health professional discussions about CREDENCE results.

Napp therefore respectfully disagreed with the Panel's ruling that the presentation '… did not make it clear how the results sat within the licenced indication, including that a sub-population of patients sat outside the licenced indication'. Napp referred in detail to three slides in the presentation to support its submission regarding the study population in relation to the product licence.

Napp noted that the Panel stated that the final slide 38 '…bore the appearance of promotional material'. Napp submitted that the slide was not promotional material, but a factual summary slide of the most important CREDENCE efficacy (primary and secondary outcomes) and key safety (no increase in lower-limb amputation [LLA] or bone fractures) results. The slides, including the concluding summary slide were all non-promotional and the results were not product claims. The colours used on this slide were not the Invokana (canagliflozin) brand colours and were used as high-impact visual cues to highlight the summary of the data results:

1 The red/green/yellow colours used did not appear on any of the Napp promotional materials for Invokana – these were not 'brand colours'. These colours were used for emphasis and simply to make the information prominent.

2 After a presentation of technical clinical data, this slide was intended to provide a straightforward and accessible summary of the key clinical trial findings.

Napp noted that the Panel commented on what it suggested was a 'strap line', at the bottom of the slides 'Credence to move medicine forward'. The bottom of the slide design used a black background and white kidney shape with 'TV +' alongside and below this was an internal Napp company wording derived from the corporate company vision which was to 'move medicine forward' – hence 'CREDENCE TO MOVE MEDICINE FORWARD'. Napp submitted that this was not a promotional claim. The Panel did not mention the second part of the strapline 'Episode one', and did not explain its specific concern with this wording. The intent of the 'Episode one' wording was specifically included to make it clear to the employees that this training event was only intended to provide educational information for them to understand what was happening surrounding the clinical impact of the CREDENCE trial. Further events (eg episode 2) would be planned as and when a licence variation was approved.

Napp submitted that it was important to understand that prior to this training day, the sales force was mandated to study 3 online modules, including completing validation questions. The online module (Renal Module UK/DIA-19019b Module 3 CREDENCE Trial Design, rationale and baseline characteristics) was most relevant as this was fresh in the sales force minds' when being presented the educational training-day slides of the CREDENCE Results. Module 3 comprised 37 online 'pages'. Page 6 (red box and table 1 below) was very clear about the CREDENCE patient inclusion criteria and sub-populations such that it stated that 'only 40% of the study population were within the canagliflozin product licence':

'INCLUSION CRITERIA

Key inclusion criteria were:[7,8]

- T2D with HbA1c 6.5 – 12% with eGFR ≥ 30 to <90 ml/min per 1.73m^2 (ie stage 2 or 3 CKD)*
- On a stable maximum tolerated labelled daily dose of an ACEi or ARB for at least 4 weeks prior to randomisation
- Urine albumin to creatinine ratio (UACR) of > 300 to ≤ 5,000 mg/mmol)

*To investigate the impact of canagliflozin on the progression of CKD, patients were recruited such that ~ 60% of the study population had eGFR 30 – 59 ml/min/1.73m^2 (ie CKD stage 3) at study entry – therefore only 40% of the study population were within the canagliflozin product licence. To review the licenced indication of canagliflozin in patients with CKD please see table below

Table 1 – Licensed indication of Invokana (canagliflozin) in patients with T2D based on renal function[10]

Renal function	Invokana licence
eGFR ≥ 60 ml/min/1.73m^2	Initiate canagliflozin at 100mg once daily. In patients tolerating canagliflozin 100mg once daily and need tighter glycaemic control, the dose can be increased to 300mg once daily.
eGFR 45-59 ml/min/ 1.73m^2	Do not initiate canagliflozin. However, in patients tolerating canagliflozin whose eFGR falls persistently below 60 ml/min/1.73m^2, adjust dose (or maintain it at) 100mg/day.
eGFR < 45 ml/min/1.73m^2 (persistently)	Discontinue canagliflozin*

* canagliflozin should not be used in patients with end-stage renal disease or in patients on dialysis as it is not expected to be effective.'

Napp submitted that one of the 10 validation questions for this module tested this knowledge (page 37 of this module). The test was taken by all Napp sales persons on completion of each training module. The relevant question was what proportion of the CREDENCE study

population falls within the canagliflozin product licence with a choice of four answers, 40%, 50%, 60% and 30%.

In summary, Napp appealed the Panel's ruling of a breach of Clause 15.9 as it had not advocated, either directly or indirectly, any course of action by the sales force which would be likely to lead to a breach of the Code. Napp submitted it had maintained high standards by providing the salesforce with educational training for their own knowledge only and for its briefing material which was sent before the training and further reinforced on the training day. Napp therefore appealed the Panel's ruling of a breach of Clause 9.1.

APPEAL BOARD RULING

The Appeal Board noted that Clause 15.9 included that 'Briefing material must not advocate, either directly or indirectly, any course of action which would be likely to lead to a breach of the Code. The supplementary information stated that 'The detailed briefing material referred to in this clause consists of both the training material used to instruct medical representatives about a medicine and the instructions given to them as to how the product should be promoted'. In the Appeal Board's view, a relevant omission in briefing material might mean that it indirectly advocated a course of action likely to lead to a breach of the Code.

The Appeal Board noted that whilst it was appropriate to brief and educate representatives on relevant new trial data such an activity had to comply with the requirements of the Code. The Appeal Board noted that at the appeal Napp described the representatives as very excited about the data. In such circumstances it was especially important to be very clear about how representatives could use the learnings from such training, particularly when it related to new data which would be of interest to health professionals etc.

The Appeal Board noted Napp's submission that the presentation at issue 'CREDENCE RESULTS!' (ref UK/INV-19124) was given alongside others on diabetic kidney disease, refresher training and comparisons of the renal results within the CANVAS trial at a one day training session with representatives in May 2019. The other presentations were not before the Appeal Board in the papers for this case and nor was an agenda for the meeting.

The Appeal Board noted in April 2019 Napp sent its representatives a Credence briefing document (UK/INV-19097) and asked the representatives to indicate that they had read and understood the briefing. The Appeal Board noted that there was thus around a month in between the provision of the briefing material and the presentation in question. In the Appeal Board's view, Napp could not rely on caveats in the briefing material to qualify the presentation at issue as implied by the company representatives at the appeal. The presentation had to be capable of standing alone in relation to the requirements of the Code.

In the Appeal Board's view, from the totality of the material before it, it appeared that the sales force had not received a clear and consistent message about whether they could discuss the data with health professionals. The representatives had also been mandated to study a 'Diabetes Training Hub – Renal Module 3 – Credence Design' (ref UK/DIA-19019b) prior to attending the training day in May 2019. The Appeal Board noted that a page in the module included a statement in a prominent red box that 'Only 40% of CREDENCE study population falls within the current canagliflozin licence. Refer to study briefing materials and your MSL prior to discussing the trial with customers'. The Appeal Board did not consider that this statement in Napp's training module clearly reflected Napp's submission that the field force

could not proactively talk about CREDENCE. Similarly, the Appeal Board queried whether following the Credence briefing, entitled 'Invokana Communication' (UK/INV-19097) about reactive responses and the trial being stopped early might solicit questions about the study results. In this regard the Appeal Board noted that neither the Training module 3 nor the Credence briefing material were the subject of the appeal. They, nonetheless, provided important background context.

The Appeal Board noted that whilst the introductory slide for the training presentation stated that the presentation was 'For internal use only,' this did not appear on the other slides. Other training material provided by Napp included this at the bottom of the pages. Noting that only 40% of the CREDENCE patient population was within the licensed indications for Invokana, the Appeal Board considered that it would have been helpful to have included the statement 'For internal use only' on every slide.

The Appeal Board noted and agreed with the Panel's concerns about the final slide in the presentation which, in its view, bore the appearance of promotional material rather than educational material. That the colours used were not brand colours did not mean that the impression of the page was not promotional as implied by the company representatives at the appeal. The slide featured a prominent red triangle, divided horizontally into thirds, each third featured a promotional claim in prominent green font. The top third of the triangle read '30% Reduction in Death or Dialysis'. A horizontal red arrow adjacent to the claim led to a prominent claim in black font within an irregular yellow star which read 'FIRST AND ONLY SGLT2i with renal outcome data'. The strap line at the bottom of each slide read 'Credence to move medicine forward, Episode 1'. This strap line appeared on all the slides, other than the introductory slide. In the Appeal Board's view, the take home message for the representatives was in relation to the claims about CREDENCE and its results as stated on the final slide rather than the fact that they could not discuss CREDENCE results externally.

The Appeal Board noted that in response to a question the representatives from Napp at the appeal confirmed that there was no script for the presentation at issue and no transcript was available. Napp submitted that during the training presentation the representatives were verbally briefed on what they could and could not do.

The Appeal Board however did not consider that the presentation at issue made it sufficiently clear how the results sat with the licensed indication, including that a sub population of patients were outside the licensed indication (60%). The slides did not explicitly state that the CREDENCE trial data should not be discussed with health professionals. The Appeal Board considered that this could have been easily stated in the presentation. It was not sufficient to rely on the April briefing in this regard as submitted by Napp and referred to above.

The Appeal Board noted the company's submission about the use of visual motifs in the presentation and verbal comments to emphasis certain points and as a means of engaging the audience. Whilst the Appeal Board considered that such an approach was not unacceptable it was nonetheless important that those points necessary for Code compliance were an integral part of the presentation.

The Appeal Board considered that, on balance, the presentation at issue failed to make it explicitly clear how representatives should discuss the CREDENCE data with health professionals. The failure to explicitly include the appropriate caveats throughout in relation to the CREDENCE data and that the concluding slide contained strong promotional claims about

renal outcome data meant that it advocated a course of action that was likely to lead to a breach of the Code. The Appeal Board consequently upheld the Panel's ruling of a breach of Clause 15.9. The appeal on this point was unsuccessful.

The Appeal Board noted its comments and ruling above and considered that these amounted to a failure to maintain high standards and consequently upheld the Panel's ruling of a breach of Clause 9.1 in relation to the briefing material. The appeal on this point was unsuccessful.

Complaint received **5 June 2019**

Case completed **10 June 2020**