CASE AUTH/3458/1/21 *NO BREACH OF THE CODE*

ANONYMOUS, CONTACTABLE HEALTH PROFESSIONAL v NAPP

Alleged off-licence promotion of Invokana

A contactable complainant who described him/herself as a concerned UK health professional complained about the promotion of Invokana (canagliflozin) by Napp Pharmaceuticals Limited. The material at issue was a video hosted on the Diabetes On The Net website entitled 'CREDENCE: Type 2 Diabetes Management – A New Perspective. Protect the kidney to protect the heart' (ref UK/INV-20107ab, August 2020). The complainant provided a link to a webpage (ref UK/INV-20107ac, September 2020) which included details about the video in question and a link to it. The video detailed the results from the CREDENCE (Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation) trial.

Invokana, a sodium-glucose co-transporter-2 (SGLT2) inhibitor, was indicated for the treatment of certain adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise.

Section 4.1 of the Invokana summary of product characteristics (SPC) (Therapeutic indications) also referred readers to other sections of the SPC for study results on glycaemic control, renal events and cardiovascular events. Section 5.1 stated that improvement in glycaemic control and reduction of cardiovascular and renal morbidity and mortality were integral parts of the treatment of type 2 diabetes.

The complainant alleged that the website did not mention that Invokana was only for adults with type 2 diabetes, not children. The complainant submitted that without providing clarification as to who could be treated, the medicine could be prescribed off-licence.

The complainant did not consider that adequate safety information had been provided, such as how the dose should be reduced or that Invokana should not be used in certain severities of renal failure - which was extremely salient in a website that, given the slogan 'protect the kidney to protect the heart', was purporting a reno-protective effect of Invokana and this was not a licenced indication.

The complainant referred to one slide entitled 'Until recently, licensed renal thresholds for use of SGLT2 [inhibitors] have been based on glycaemic efficacy'. The complainant alleged that the slide misrepresented competitors; the title and body of the text stated one thing, but the small footnote 'No dose adjustments based on renal function are needed for dapagliflozin, 10mg is the highest recommended dose for dapagliflozin', meant that it was not true for that medicine.

The complainant submitted that most trial outcomes were not licensed indications and the audience was not made aware that at best these were added benefits, rather than a reason to use the treatment. The complainant referred to a slide which included a

number of hazard ratios in favour of canagliflozin vs placebo: these being cardiovascular death or hospitalised heart failure (p=0.0001), hospitalised heart failure (p=0.0003), cardiovascular death, myocardial infarction or stroke (p=0.0121).

The complainant also referred to a slide entitled 'Use of Canagliflozin in Clinical Practice for Patients with [Type 2 Diabetes]' which listed canagliflozin as a treatment for three conditions - cardiovascular disease, kidney disease and diabetes. The complainant alleged that this was blatant off-licence promotion – Invokana was only licensed for diabetes, not merely for patients who happened to have type 2 diabetes.

The detailed response from Napp is given below.

The Panel noted that the webpage included the Napp diabetes, Credence trial, and Invokana logos at the top and a link to the Invokana prescribing information. The webpage also included an image of the on demand presentation's title slide headed 'CREDENCE: Type 2 Diabetes Management - A New Perspective Protect the kidney to protect the heart' and included an image of a heart shaped lollipop with kidneys within it. The introduction to the video stated 'What does the CREDENCE trial mean for the management of diabetic kidney disease (DKD) in type 2 diabetes mellitus (T2DM) for specialists?'. It went on to explain that the promotional video which was aimed specifically at renal, diabetes and cardiology specialists, looked at the CREDENCE trial and assessed how Invokana (canagliflozin) might change the management of DKD in type 2 diabetes in the secondary care setting. The video was described as giving a unique insight into the CREDENCE trial design and results from two of the lead investigators; and how the findings of CREDENCE translated into the specialist setting. The Panel noted that the video, which appeared to be aimed at a secondary care audience and lasted just over 1 hour, consisted of three sessions. The Panel noted that the presentation overall explored what the renal results from the CREDENCE trial meant for the management of diabetic kidney disease in adult patients with type 2 diabetes.

It appeared to the Panel that if a reader clicked to view the video from the above webpage, a slide (ref UK/INV-20107p, July 2020) which stated, *inter alia*, that Invokana was indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise followed by 'For treatment of diabetic kidney disease (DKD) in adults with T2DM as add-on to standard of care, a dose of 100mg once daily should be used. Please see Invokana SmPC section 4.2 for details about dosing' was shown before the main presentation began.

With regard to the complainant's allegation that the website did not mention that Invokana was only for adults with type 2 diabetes, not children, the Panel noted that there was no specific mention or impression given on the webpage in question that Invokana was licensed to treat children with type 2 diabetes. Although it might have been helpful for the indication to have been included on the webpage itself, it was included within the linked prescribing information, the video slide before the presentation began and at additional timepoints within the video. The Panel therefore did not consider that the webpage or video in question was misleading such that it promoted the use of Invokana in children as alleged. No breaches of the Code were ruled.

With regard to a slide entitled 'Until recently, licensed renal thresholds for use of SGLT2 [inhibitors] have been based on glycaemic efficacy', .the Panel noted that although it was highly unusual to present out-dated prescribing details, the context in which the side was used and the commentary which accompanied it meant that, in the Panel's view, the slide was not necessarily unacceptable. The slide followed a discussion of a patient case study and was used to illustrate that until recently, due to his deteriorating kidney function (currently 39ml/min/1.73m^2) the patient, who was at high risk of a cardiovascular event, would not have been able to be treated with an SGLT2 inhibitor but that he would have qualified for inclusion in the CREDENCE trial. The slide featured a graphic which showed that for patients with an eGFR of between 60 – 90ml/min/1.73m^2, SGLT2 inhibitors could be initiated and titrated up according to glycaemic control. Four SGLT2s were so listed with the starting dose and the maximum dose for titration stated for three of them. The fourth SGLT2 inhibitor listed was dapagliflozin with only a 10mg dose stated. A footnote read, 'No dose adjustments based on renal function are needed for dapagliflozin, 10mg is the recommended highest dose for dapagliflozin'. The Panel considered that the footnote confirmed the single dose for dapagliflozin as stated in the graphic – it did not qualify it. It was clear from the main body of text that there was only one dose for dapagliflozin compared with the other three SGLT2 inhibitors with doses that could be titrated upwards and so in that regard the Panel did not consider that the information was misleading. No breach of the Code was ruled.

The Panel noted that the complainant alleged that one of the presenters stated that there were benefits to patients' renal outcomes without mentioning that it was not a licensed indication. The complainant had not provided details of what was said or by whom and the Panel considered that the complainant had not made out his/her allegation in that regard. It was not for the Panel to infer reasons to support a complainant's allegations. The Panel therefore ruled no breaches of the Code in that regard.

The Panel noted that the complainant alleged that two slides from the video in question, were examples of off-licence promotion. The Panel noted that the first slide included a summary of the cardiovascular trial outcomes including, *inter alia*, cardiovascular death or hospitalised heart failure; hospitalised heart failure; cardiovascular death, myocardial infarction or stroke. The second slide was titled 'Use of Canagliflozin in Clinical Practice for Patients With T2DM' followed by three statements: Canagliflozin as Treatment for Cardiovascular Disease; Canagliflozin as Treatment for Kidney Disease; and Canagliflozin as Treatment for Diabetes. Below these statements were the letter C, K and D. Letter C which was detailed as standing for cardiology and was associated with an image of a heart, K for kidney associated with an image of the kidneys and D for diabetes associated with an image of a pancreas.

The Panel considered that it was not unacceptable for companies to promote the additional benefits that might be afforded from treatment with a particular medicine provided that those benefits were clearly set within the context of the licensed indication. The primary reason to prescribe must be made clear.

The Panel noted from Section 4.1 of the Invokana 100mg SPC that the licensed indication was:

> **'for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise**

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications

- in addition to other medicinal products for the treatment of diabetes

For study results with respect to combination of therapies, effects on glycaemic control, cardiovascular and renal events, and the populations studied, see sections 4.4, 4.5 and 5.1.'

Section 5.1 of the SPC stated, below the heading 'Clinical efficacy and safety', that improvement in glycaemic control and reduction in cardiovascular and renal morbidity and mortality were integral parts of the treatment of type 2 diabetes.

The Panel noted that section 4.2 (Posology and method of administration) of the Invokana 100mg SPC stated under the heading 'Renal impairment' that, *inter alia*, 'for treatment of diabetic kidney disease as add on to standard of care (eg ACE-inhibitors or ARBs [angiotensin receptor blockers]), a dose of 100mg canagliflozin once daily should be used' and further included dose adjustment recommendations depending on the patient's eGFR or CrCl.

The Panel noted Napp's submission that renal protection information was included within the Invokana SPC following the outcome data from the CREDENCE trial and that the Invokana 100mg SPC now reflected the extended indication to treat diabetic kidney disease in type 2 diabetes patients as add on to standard of care.

In the Panel's view, it was thus not necessarily unacceptable to refer to the renal benefits of Invokana in type 2 diabetes patients. Similarly, nor was it necessarily unacceptable to refer to its cardiovascular benefits; both appeared to be an integral part of the treatment of type 2 diabetes.

The Panel considered that although the slide summarising the cardiovascular outcomes did not refer to type 2 diabetes, it noted Napp's submission that one of the objectives of session 2 'CREDENCE: bringing the data to life', in which the slide at issue appeared was to present the detailed study results including both the renal and cardiovascular endpoints from the study. Further the session began with describing the study and its design including that one of the key inclusion criteria was type 2 diabetes mellitus. The Panel noted that the slide in question followed a slide which discussed the incidence of hospitalised heart failure in clinical trials with SGLT2 inhibitors and the presenter stated that data from the CREDENCE trial showed that people with evidence of kidney damage in the presence of diabetes were not only at increased risk of developing kidney failure but also at the highest risk of developing heart failure too. The Panel further noted that the speaker highlighted that the slide depicting hazard ratios represented a summary of the secondary cardiovascular outcomes from the CREDENCE study. In the Panel's view, viewers of the video would, therefore, view the cardiovascular outcomes on the slide in question in the context of type 2 diabetes. The Panel did not consider that the complainant had established that the slide at issue promoted Invokana in a manner that was not in accordance with the terms of its marketing authorisation or was inconsistent with the SPC with regards to its cardiovascular benefits in type 2 diabetes patients as alleged; no breach of the Code was ruled. Nor was the slide in the context of the overall presentation misleading in this regard and the Panel ruled no breach of the Code.

The complainant also referred to a slide headed 'Use of Canagliflozin in Clinical Practice for Patients with [Type 2 Diabetes]'. The slide listed canagliflozin as treatment for cardiovascular disease, kidney disease and diabetes, in that order. Whilst the Panel was concerned that diabetes appeared last in the list and that below this list D(diabetes) with the associated pancreas image also appeared last following C(cardiology) and K(kidney) and the associated heart and kidney image respectively, the Panel noted that the title of the slide clearly referred to the use of canagliflozin in clinical practice for patients with type 2 diabetes. The presenter stated that Invokana had multiple benefits for patients with type 2 diabetes and especially those with evidence of kidney disease. It was stated that the CREDENCE trial had demonstrated that treatment with Invokana resulted in a reduced risk of major cardiovascular events and heart failure, a reduced risk of renal failure and transplantation and that it had a glucose lowering effect. It would be clear to viewers that the treatment of cardiovascular disease and kidney disease was in the context of the treatment of type 2 diabetes patients. The Panel, therefore, did not consider that the complainant had established that the slide at issue promoted Invokana in a manner that was not in accordance with the terms of its marketing authorisation or was inconsistent with its SPC with regards to its renal and cardiovascular benefits in type 2 diabetes patients as alleged; nor was the slide misleading in this regard. The Panel ruled no breaches of the Code.

The Panel noted that the complainant alleged that the webpage which hosted the on demand video claimed that Invokana had a reno-protective effect which was off-licence. In that regard the complainant also referred to the slogan 'protect the kidney to protect the heart' which appeared as part of the presentation's title following 'CREDENCE: Type 2 Diabetes Management – A New Perspective'. The Panel considered that the complainant bore the burden of proof and had not established, on the balance of probabilities, that either the webpage or the associated video presentation promoted Invokana in a manner that was not in accordance with the terms of its marketing authorisation or was inconsistent with its SPC with regards to its renal benefits in type 2 diabetes patients as alleged, nor was the webpage or the presentation overall misleading in this regard. The Panel ruled no breaches of the Code.

The Panel considered both the webpage advertising the video and the video presentation itself in relation to the complainant's general concern that not enough safety information had been given on the webpage.

The Panel noted that whilst the webpage referred to the management of diabetic kidney disease in type 2 diabetes mellitus and included the strapline 'Protect the kidney to protect the heart', it did not include specific details with regard to treatment of patients with renal impairment with Invokana or provide any specific dosage instructions. The webpage encouraged readers to view the video to find out about what the CREDENCE trial results might mean in practice. Further, the information was included within the Invokana prescribing information linked from the webpage and the agenda for session 3 referred to dosing considerations highlighting that it was a topic that would be covered in the presentation. The Panel noted the secondary care audience and that Invokana had been in use since 2013 when the dosage in renal impairment was more restrictive than currently. The Panel did not consider that, particularly given its purpose and content, the webpage was misleading as alleged. No breach of the Code was ruled.

The Panel noted Napp's submission that in session 3 of the presentation which discussed how the CREDENCE data translated in a specialist clinical setting, the indication for Invokana was discussed in detail and clearly highlighted the dose adjustments required for Invokana based on renal function as set out in its SPC. The Panel noted, however, that the slide displayed before the presentation began (ref UK/INV-20107p, July 2020), in addition to stating that Invokana was licensed for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise, also stated, with equal prominence and on a separate line, 'For treatment of diabetic kidney disease (DKD) in adults with [type 2 diabetes] as add-on to standard care, a dose of 100mg once-daily should be used. Please see Invokana SPC section 4.2 for details about dosing'.

The Panel considered that the statement about the treatment of diabetic kidney disease on this slide implied that all adult type 2 diabetes patients with diabetic kidney disease could be given 100mg Invokana which was not so. The Panel noted that a table of dose adjustment recommendations in Section 4.2 of the Invokana SPC showed that although patients with an estimated glomerular filtration rate (eGFR) of more than 30ml/min/1.73m^2 could be initiated on Invokana 100mg, those with an eGFR of less than 30ml/min/1.73m^2 could not be initiated on Invokana although if they had already started therapy at 100mg then it could be maintained. The Panel further noted that beneath the heading Renal impairment in Section 4.4 of the Invokana SPC, Special warnings and precautions for use, it stated 'The efficacy of canagliflozin for glycaemic control is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment (see section 4.2)'. It further stated that monitoring of renal function was recommended prior to initiation of canagliflozin and at least annually, thereafter (see Sections 4.2, 4.8, 5.1, and 5.2) and before initiation of concomitant medicines that might reduce renal function and periodically thereafter.

The Panel considered that the statement regarding the use of Invokana 100mg in diabetic kidney disease on the slide (ref UK/INV-20107p, July 2020) that displayed before the presentation began was thus misleading. That readers were referred to Section 4.2 of the SPC for details about dosing and a summary of the SPC dose adjustments based on renal function were highlighted towards the end of the presentation in session 3 (starting at 42.50 minutes) was insufficient to negate the immediate misleading impression that all adult type 2 diabetes patients with diabetic kidney disease could be given 100mg Invokana. A breach of the Code was ruled. The Panel considered that high standards had not been maintained and a breach of the Code was ruled. The Panel considered that the claim put type 2 diabetes patients with diabetic kidney disease and an eGFR <30ml/min/1.73m^2 at risk of being initiated with Invokana 100mg when the SPC stated that they should not be. The Panel considered that it was potentially prejudicial to patient safety and a breach of Clause 2 was ruled. These rulings were appealed by Napp.

The Panel noted that the Code stated that information and claims about adverse reactions must reflect available evidence or be capable of substantiation by clinical experience. It must not be stated that a product had no adverse reactions, toxic hazards or risks of addiction or dependency. The word 'safe' must not be used without qualification. The Panel did not consider that the complainant had raised an allegation in that regard. Nonetheless, the Panel noted Napp's submission that Session 2 of the video presentation discussed in detail the safety information of Invokana from the CREDENCE

trial including the adverse events experienced. The Panel therefore ruled no breach of the Code.

Upon appeal by Napp, the Appeal Board noted the content of the slide at issue which was shown for several seconds before the main presentation of over 1 hour duration began.

The Appeal Board considered that when treating diabetes patients with renal impairment health professionals would be especially cautious and were likely to consult the SPC before prescribing. In that regard the Appeal Board noted the reference on the slide at issue to prescribing information being available at the end of the presentation. In addition, the slide included '…Please see Invokana SmPC section 4.2 for details about dosing'. The Appeal Board considered that whilst Napp had chosen to refer prescribers to Section 4.2 on dosing it might have been clearer, given the topic of the presentation, to include a statement summarising the dose adjustment recommendations according to eGFR from Section 4.2 of the SPC. However, the Appeal Board noted that the slide only appeared briefly and that later in the presentation a summary of the SPC dose adjustments based on renal function and that certain patients could continue on Invokana but should not be initiated on the medicine was included. Taking all the circumstances into account the Appeal Board considered that in the context of the video, the slide at issue did not misleadingly imply that all adult type 2 diabetes patients with diabetic kidney disease could be given 100mg Invokana. The Appeal Board ruled no breach of Code. Consequently, the Appeal Board ruled no breach of the Code including Clause 2. The appeal on all points was successful.

A contactable complainant who described him/herself as a concerned UK health professional complained about the promotion of Invokana (canagliflozin) by Napp Pharmaceuticals Limited. The material at issue was a video hosted on the Diabetes On The Net website entitled 'CREDENCE: Type 2 Diabetes Management – A New Perspective. Protect the kidney to protect the heart' (ref UK/INV-20107ab, August 2020). The complainant provided a link to a webpage (ref UK/INV-20107ac, September 2020) which included details about the video in question and included a link to it. The video detailed the results from the CREDENCE (Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation) trial.

Invokana, a sodium-glucose co-transporter-2 (*SGLT2*) inhibitor, was indicated for the treatment of certain adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise.

Section 4.1 of the Invokana summary of product characteristics (SPC) (Therapeutic indications) also referred readers to Sections 4.4, 4.5 and 5.1 for study results on glycaemic control, renal events and cardiovascular events. Under a heading of 'Clinical efficacy and safety' in Section 5.1, it was stated that improvement in glycaemic control and reduction of cardiovascular and renal morbidity and mortality were integral parts of the treatment of type 2 diabetes.

COMPLAINT

The complainant alleged that the website did not mention that Invokana was only for adults with type 2 diabetes, not children. The complainant submitted that without providing clarification as to who could be treated, the medicine could be prescribed off-licence.

The complainant did not consider that adequate safety information had been provided, such as how the dose should be reduced or indeed that Invokana should not be used in certain severities of renal failure - which was extremely salient in a website that, given the slogan 'protect the kidney to protect the heart', was purporting a reno-protective effect of Invokana when Invokana did not have any licensed indication to have a reno-protective indication (again off-licence promotion). The complainant further noted that the presenter stated there were benefits to patients to renal outcomes but did not mention that this was not a licenced indication.

The complainant referred to one slide entitled 'Until recently, licensed renal thresholds for use of SGLT2 [inhibitors] have been based on glycaemic efficacy'. The slide featured a graphic which showed that for patients with an estimated glomerular filtration rate (eGFR) of between 90 and 60ml/min/1.73m^2, SGLT2 inhibitors could be initiated and titrated up for glycaemic control. The SGLT2 inhibitors listed in a green box (Initiate treatment) were canagliflozin (100mg-300mg), empagliflozin (10mg-25mg), ertugliflozin (5mg-15mg) and dapagliflozin (10mg). For patients with an eGFR of between 60 and 45ml/min/1.73m^2, then SGLT2 inhibitors listed in an orange box (Do not initiate treatment) could be continued if already initiated with doses of canagliflozin (100mg), empagliflozin (10mg), ertugliflozin (5mg or 15mg) and dapagliflozin (10mg). For patients with an eGFR of between 45 and 30ml/min/1.73m^2 it was stated that SGLT2 inhibitors should not be initiated and any current treatment with them should be stopped (red box). The complainant alleged that the slide misrepresented competitors; the title and body of the text stated one thing, but the small footnote 'No dose adjustments based on renal function are needed for dapagliflozin, 10mg is the highest recommended dose for dapagliflozin', meant that it was not true for that medicine.

The complainant submitted that most trial outcomes were not licensed indications and there was nothing present on the slides to make the audience aware that at best these were added benefits, rather than a reason to use the treatment. In that regard, the complainant referred to a slide which, *inter alia*, reported the hazard ratios of the following outcomes in favour of canagliflozin vs placebo: cardiovascular death or hospitalised heart failure (p=0.0001), hospitalised heart failure (p=0.0003), cardiovascular death, myocardial infarction or stroke (p=0.0121).

The complainant also referred to a slide entitled 'Use of Canagliflozin in Clinical Practice for Patients with [Type 2 Diabetes]' which listed canagliflozin as a treatment for three conditions - cardiovascular disease, kidney disease and diabetes. The complainant submitted that only one of those conditions was a licensed indication - itself with caveats. The complainant alleged that this was blatant off-licence promotion – Invokana was only licensed for diabetes, not merely for patients who happened to have type 2 diabetes.

When writing to Napp, the Authority asked it to consider the requirements of Clauses 3.2 and 7.2 in relation to the allegations regarding promoting off-licence and unlicensed indications and the requirements of Clauses 7.2 and 7.9 in relation to the allegations about safety information. The company was also asked to bear in mind the requirements of Clauses 9.1 and 2.

RESPONSE

Napp noted the complainant's allegation that the video did not state that Invokana was only for use in adults with type 2 diabetes, not children and that without clarification as to who could be treated, was promoting off-licence.

Napp submitted that the promotional nature of the page on the Diabetes On The Net website (diabetesonthenet.com) referred to by the complainant was identified at the top of the page. The webpage was an advertisement for a promotional video about Invokana (canagliflozin) renal data as part of type 2 diabetes management. As required by the Code for digital materials appearing on the internet (Clause 4.6) the licensed indication information was available on the site via a single-click link to the Invokana prescribing information. The prominent link to the prescribing information was clearly visible at the top right in bold red capitals above the Invokana brand logo (screenshot provided (ref UK/INV-20107ac)). The prescribing information (copy provided) contained relevant abbreviated information from the SPC related to the indication, dosage and method of use of Invokana and clearly stated that Invokana was indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise.

Furthermore, the first slide of the video presentation starting at 00:00 minutes (screenshot provided (ref [UK/INV-20107p, July 2020]) gave the full licensed indication, which clearly stated that Invokana was indicated for the treatment of adults. Session 3 of the presentation discussed how the CREDENCE data translated in a specialist clinical setting, the indication for Invokana was discussed in detail, and a slide stating that Invokana was indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise (screenshot provided (ref UK/INV-20107ab), starting at 42.50 minutes). The prescribing information was also provided at the end of the presentation (screenshot provided, starting at 01.05.38 minutes). Napp submitted that it had thus clearly made the intended health professional audience aware of the licensed indication for Invokana and denied breaches of Clauses 3.2 and 7.2.

With regard to the complainant's comments about the provision of safety information, use in renal failure, renal protection and off-licence promotion, Napp submitted that the webpage was an advertisement for a promotional video about Invokana renal data as part of type 2 diabetes management. The Code did not require digital material to provide prescribing information on the webpage itself, but that it had to be available via a prominent single-click link. As noted above, the prescribing information was available via a one-click link on the webpage (screenshot provided (ref UK/INV-20107ac)). The prescribing information provided abbreviated information from the SPC related to the dosage and method of use of Invokana relevant to dosage adjustment recommendations in renal impairment. As tabulated in the 'Dosage & Administration' section of the prescribing information, for patients with an eGFR <30ml/min/1.73m^2, canagliflozin could not be initiated but might be continued with a dosage of 100mg if the patient was already taking it.

Furthermore, session 2 of the video presentation (presentation recording provided [UK/INV-20107ab] starting at 17:41 minutes), also discussed in detail the safety information of Invokana from the CREDENCE trial.

In addition, regarding how 'the [Invokana] dose should be reduced or indeed the treatment should not be started in certain severities of renal failure', Napp noted that the first slide of the video presentation ([UK/INV-20107p], starting at 00:00 minutes, copy provided) referred to the dosage for the treatment of diabetic kidney disease (DKD) in adults with type 2 diabetes, and as

per the comments above, in session 3 of this presentation which discussed how the CREDENCE data translated in a specialist clinical setting, the indication for Invokana was discussed in detail ([UK/INV-20107ab], starting at 42.50 minutes copy provided) and clearly highlighted the dose adjustments required for Invokana based on renal function. The prescribing information was also provided at the end of the presentation ([UK/INV-20107ab] copy provided, starting at 01.05.38 minutes).

With regard to the complainant's reference to reno-protection and off-licence promotion, Napp noted that renal protection information was included within the Invokana SPC and explained that on 2 July 2020, the European Commission (EC) approved the extension of the indication of Invokana 100mg to include the renal outcomes data from the CREDENCE trial; a dedicated renal outcomes trial in patients with diabetic kidney disease and type 2 diabetes. The results of the trial were considered robust and clinically relevant. The European Medicines Agency (EMA) was of the view, upon granting the indication extension, that the already approved indication 'treatment of patients with insufficiently controlled type 2 diabetes' covered both the aim of the treatment, which was not limited to glycaemic control but included other treatment goals such as the prevention of worsening of diabetic complications and the target population (patients with diabetic kidney disease) were not excluded from the current indication. It was considered that a separate indication for the treatment of diabetic kidney disease in Section 4.1 of the SPC was not warranted. The indication for insufficiently controlled diabetes now included the management of diabetic kidney disease for Invokana. In that regard, Napp provided a copy of the May 2020 Invokana European Public Assessment (ePAR) and referred in particular to page 63, section 2.4.3, page 93, sections 3.7.3 and 3.8, and page 94, section 4.

Subsequently, Invokana 100mg was now approved with an extended indication to treat diabetic kidney disease in type 2 diabetics with severe albuminuria (urinary albumin:creatinine ratio >30mg/mmol (>300mg/g)) as add on to standard of care (eg ACE inhibitors or angiotensin receptor blockers). The Invokana 100mg SPC (copy provided) detailed that indication extension in Section 4.1 which now included 'renal events'. Section 4.2 (posology) of the SPC now also reflected that type 2 diabetes patients with an eGFR of ≥45 to <60ml/min/1.73m^2 could be initiated on Invokana 100mg. In addition, type 2 diabetes patients with severe albuminuria (urinary albumin:creatinine ratio >30mg/mmol (>300mg/g)) and an eGFR ≥30ml/min/1.73m^2 could now be initiated on Invokana 100mg and maintained on treatment until dialysis or renal transplantation. Finally, the renal outcomes data from the CREDENCE trial were incorporated within section 5.1 of the licence for Invokana. Therefore, renal protection information was included within the Invokana SPC.

Napp noted that in Case AUTH/3294/1/20, Promotion of Invokana, it was stated in the ruling that 'The Panel considered that, on balance, taken as a whole bearing in mind that health professionals would be aware of the need to consider the impact of diabetes on cardiovascular and renal function….'.

Napp therefore refuted breaches of Clauses 3.2, 7.2 and 7.9 as it had clearly made the health professional audience aware of the safety information, how Invokana should be used dependent on renal function and the claims purporting to the reno-protective effects of canagliflozin on the webpage in question were substantiated, were not misleading and were consistent with the SPC.

With regard to the strapline 'protect the kidney to protect the heart', Napp noted that the original 2013 licensed indication for Invokana (and other SGLT2 inhibitors) was focused on glycaemic

(ie blood sugar) control. Following the publication of the phase 3 canagliflozin cardiovascular outcomes trial (CANVAS Program) in 2017 it was recognised that the treatment goals should also extend beyond blood glucose to address other significant diabetes complications, including cardiovascular protection. To reflect that, the licence was updated in 2018 by changing '…to improve glycaemic control' to '…for the treatment of adults with insufficiently controlled type 2 diabetes…'.

Napp noted that in Case AUTH/3033/4/18, Promotion of Victoza, it was stated in the Panel ruling that 'The Panel considered that the important factor was that the patient had type 2 diabetes. The outcome of the cardiovascular study would be of interest to those that treated type 2 diabetes. There was a change to the Victoza SPC and the company was fully entitled to draw attention to that change.'.

As explained above, following the 2019 publication of the phase 3 primary renal outcomes CREDENCE trial, Janssen-Cilag International NV (the marketing authorisation holder for Invokana) submitted a variation to include an additional indication for diabetic kidney disease (Invokana ePAR copy provided). An indication extension was approved in July 2020 to include 'For the treatment of diabetic kidney disease (DKD) as add on to the standard of care…'. Therefore, based on the information above, the canagliflozin cardiovascular and renal trials led to changes in the Invokana SPC and were highly relevant to be shared with health professionals treating type 2 diabetes. Both cardiovascular and renal outcomes were integral in the management of type 2 diabetes patients, therefore they were highly important for health professionals treating those patients and were not inconsistent with the SPC. Napp denied breaches of Clauses 3.2 and 7.2.

Napp noted that the complainant had referred to a presenter who had stated that there were benefits to patients' renal outcomes but it was unclear as to which of the three presenters the complainant was referring. Regardless of that, it was legitimate to highlight to health professionals the highly relevant renal protective benefits and the secondary cardiovascular outcomes of Invokana from the CREDENCE trial. This was the most significant development in the management of diabetic kidney disease for over 20 years (when ACE inhibitors and angiotensin receptor blockers were shown to have renal benefits in diabetes patients). The benefits to renal outcomes was an extension to the indication of SGLT2 inhibitors, including canagliflozin, and as above, it was not inconsistent with the SPC. Napp thus denied breaches of Clauses 3.2 and 7.2.

Napp noted the complainant's reference to the slide entitled '<u>Until recently,</u> licensed renal thresholds for use of SGLT2 [inhibitors] have been based on glycaemic efficacy' and stated that it was unclear as to what the complainant considered had been misrepresented. The slide factually showed how the SGLT2 inhibitors should be initiated (green box), maintained (orange box) or stopped (red box) based on renal function as measured by the eGFR. The information was fully referenced on the slide to the corresponding SPCs for the medicines listed.

Regarding the complainant's reference to a footnote about dapagliflozin, Napp stated that the information presented in the main body of the slide accurately represented how each of the SGLT2 inhibitors should be used based on a patient's renal function. In contrast to the other SGLT2 inhibitors, dapagliflozin had a single 10mg dose, whereas the rest had two available doses. The slide clearly demonstrated that between an eGFR of 60-90ml/min/1.73m^2 dapagliflozin 10mg could be initiated and between an eGFR of 45-60ml/min/1.73m^2 dapagliflozin 10mg could be maintained, but not initiated. That information was accurate and

not inconsistent with the dapagliflozin SPC for type 2 diabetes (a link to the electronic Medicines Compendium was provided). The footnote in question stated 'No dose adjustments based on renal function are needed for dapagliflozin, 10mg is the recommended highest dose for dapagliflozin'. Napp submitted that the footnote supported the main body of the text, it did not qualify any of the information presented on the slide. Napp denied a breach of Clause 7.2 as the information was accurate, balanced, fair and objective.

With regard to the complainant's submission that most trial outcomes were not licensed indications and there was nothing present on the slides to make the audience aware that at best these were added benefits, rather than a reason to use the treatment. Napp noted that he/she had referred to a summary slide which reported the hazard ratios of cardiovascular outcomes in favour of canagliflozin vs placebo and also a slide entitled 'Use of Canagliflozin in Clinical Practice for Patients with [Type 2 Diabetes]' which listed canagliflozin as a treatment for three conditions - cardiovascular disease, kidney disease and diabetes. Napp noted, however that the complainant had not been specific about which slides he/she considered should be made clear were added benefits.

Napp noted that the title of session 2 of the video was 'CREDENCE: bringing the data to life' where one of the objectives was to present the detailed study results. That session presented the efficacy (which included both the renal and cardiovascular endpoints from the study) and the safety information from the CREDENCE trial (ref UK/INV-20107ab), starting at 17.41 minutes.

At 27.27 minutes of the presentation recording (UK/INV-20107ab), the speaker highlighted that the slide depicting hazard ratios represented a summary of the secondary cardiovascular outcomes from the CREDENCE study. That slide referred to both the Invokana SPC and Mahaffey *et al* (2019) (copy provided) for which the forest plots for those endpoints were included.

The clinical safety and efficacy of Section 5.1 of the Invokana SPC included both the cardiovascular and renal outcomes from the CANVAS Program and CREDENCE trial. The SPC stated in the opening paragraph for clinical safety and efficacy that: 'Improvement in glycaemic control and reduction of cardiovascular and renal morbidity and mortality were integral parts of the treatment of type 2 diabetes'.

Napp maintained that cardiovascular and renal outcomes were highly relevant considerations to the optimum care of those with type 2 diabetes; treatment should not be solely focused on glycaemic control.

Napp noted that the complainant had referred to the slide entitled 'Use of Canagliflozin in Clinical Practice for Patients with [Type 2 Diabetes]' and stated that only one of the conditions listed was a licensed indication - itself with caveats. The complainant had alleged that the slide was blatant off-licence promotion as Invokana was only licensed for diabetes, not merely for those who happened to have type 2 diabetes.

Napp noted that the purpose of the slide at issue was to highlight the cardiorenal and metabolic efficacy for Invokana in the treatment of type 2 diabetes, rather than only focussing on glycaemic control. At 35.48 minutes of the video (UK/INV-20107ab)), the speaker stated that through CREDENCE, and other studies, there was clear cardiovascular benefits with reductions in major cardiovascular events and heart failure in patients with type 2 diabetes. In addition, that canagliflozin clearly had important kidney benefits, reducing the risk of not only the primary

composite kidney outcomes used, but of kidney failure and requiring dialysis or transplantation or leading to death. At the bottom of the slide were the words Cardiology, Kidney and Diabetes beneath which were depictions of a heart, kidneys and a pancreas respectively. Napp submitted that the 'D' for Diabetes, represented by an image of a pancreas, referred to the point that Invokana had a glucose lowering effect.

Napp submitted that the title of the slide, 'Use of Canagliflozin in Clinical Practice for Patients with [Type 2 Diabetes]', clearly indicated that this was a presentation of the use of canagliflozin in type 2 diabetes and as per the evidence provided above, a discussion of cardiovascular and renal outcomes did not constitute off-licence promotion. The reduction of cardiovascular and renal morbidity and mortality were integral parts of the treatment of type 2 diabetes and a separate indication of diabetic kidney disease was considered unwarranted by the EMA as it was already covered by the existing licence of 'insufficiently controlled type 2 diabetes'. Napp thus denied a breach of Clauses 3.2 and 7.2.

In conclusion, Napp considered that it had explained how it had maintained high standards (Clause 9.1) and made clear why it refuted breaches of Clauses 3.2, 7.2 and 7.9. Napp firmly believed that it had upheld the highest standards and had not brought discredit upon, or reduced confidence in, the pharmaceutical industry, and it thus denied a breach of Clause 2.

PANEL RULING

The Panel noted that the complainant provided a link to a webpage (ref UK/INV-20107ac, September 2020), which advertised and included a link to an on demand promotional Invokana video.

The Panel noted that the webpage included the Napp diabetes, Credence trial, and Invokana logos at the top and a link to the Invokana prescribing information. The webpage also included an image of the on demand presentation's title slide headed 'CREDENCE: Type 2 Diabetes Management - A New Perspective Protect the kidney to protect the heart' and included an image of a heart shaped lollipop with kidneys within it. The introduction to the video stated 'What does the CREDENCE trial mean for the management of diabetic kidney disease (DKD) in type 2 diabetes mellitus (T2DM) for specialists?'. It went on to explain that the promotional video which was aimed specifically at renal, diabetes and cardiology specialists, took an exclusive look at the CREDENCE trial and assessed how Invokana (canagliflozin) might change the management of DKD in type 2 diabetes in the secondary care setting. The video was described as giving a unique insight into the CREDENCE trial design and results from two of the lead investigators; and how the findings of CREDENCE translated into the specialist setting. The webpage also included the agenda. The Panel noted that according to the agenda the video, which appeared to be aimed at a secondary care audience and lasted just over 1 hour, consisted of three sessions; Session 1 (Chair's introduction The CREDENCE study and the current management of DKD in type 2 diabetes); Session 2 (CREDENCE: bringing the data to life); and Session 3 (How does the CREDENCE data translate in a specialist setting? An expert discussion). The Panel noted that the presentation overall explored what the renal results from the CREDENCE trial meant for the management of diabetic kidney disease in adult patients with type 2 diabetes. Three of the four presenters were nephrologists, and one was a consultant diabetologist.

It appeared to the Panel that if a reader clicked to view the video from the above webpage, a slide (ref UK/INV-20107p, July 2020) which stated, *inter alia*, that Invokana was indicated for the

treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise followed by 'For treatment of diabetic kidney disease (DKD) in adults with T2DM as add-on to standard of care, a dose of 100mg once daily should be used. Please see Invokana SmPC section 4.2 for details about dosing' was shown before the main presentation began.

With regard to the complainant's allegation that the website did not mention that Invokana was only for adults with type 2 diabetes, not children, the Panel noted that there was a link to the prescribing information in the top right-hand corner of the webpage in question. The prescribing information clearly stated the licensed indication for Invokana ie for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise as did the first slide before the video began. The Panel further noted Napp's submission that in addition the indication for Invokana was discussed in detail in Session 3.

The Panel noted that there was no specific mention or impression given on the webpage in question that Invokana was licensed to treat children with type 2 diabetes. In the Panel's view, although it might have been helpful for the indication to have been included on the webpage itself, it was included within the linked prescribing information and the video slide displayed before the presentation began and at additional timepoints within the video. The Panel therefore did not consider that the webpage or video in question was misleading such that it promoted the use of Invokana in children as alleged. No breach of Clauses 3.2 and 7.2 were ruled.

The Panel noted that the complainant referred to a slide (15:18) entitled 'Until recently, licensed renal thresholds for use of SGLT2 [inhibitors] have been based on glycaemic efficacy'. The Panel noted the heading of the slide, 'Until recently,…' and although it was highly unusual to present out-dated prescribing details, the context in which the side was used and the commentary which accompanied it meant that, in the Panel's view, the slide was not necessarily unacceptable. The slide followed a discussion of a patient case study and was used to illustrate that until recently (ie before clinical trials had shown the cardio-protective effects of SGLT2 inhibitors in type 2 diabetes), due to his deteriorating kidney function (currently 39ml/min/1.73m^2) the patient, who was at high risk of a cardiovascular event, would not have been able to be treated with an SGLT2 inhibitor but that he would have qualified for inclusion in the CREDENCE trial. The slide featured a graphic which showed that for patients with an eGFR of between 60 – 90ml/min/1.73m^2, SGLT2 inhibitors could be initiated and titrated up according to glycaemic control. Four SGLT2s were so listed with the starting dose and the maximum dose for titration stated for three of them. The fourth SGLT2 inhibitor listed was dapagliflozin with only a 10mg dose stated. A footnote read, 'No dose adjustments based on renal function are needed for dapagliflozin, 10mg is the recommended highest dose for dapagliflozin'. The Panel considered that the footnote confirmed the single dose for dapagliflozin as stated in the graphic – it did not qualify it. It was clear from the main body of text that there was only one dose for dapagliflozin compared with the other three SGLT2 inhibitors with doses that could be titrated upwards and so in that regard the Panel did not consider that the information was misleading. No breach of Clause 7.2 was ruled.

The Panel noted that the complainant alleged that one of the presenters in the video stated that there were benefits to patients' renal outcomes without mentioning that it was not a licensed indication. The Panel noted, however, that the complainant had not provided details of what was said or by which presenter and the Panel considered that the complainant had not made out his/her allegation in that regard. It was not for the Panel to infer reasons to support a

complainant's allegations. The Panel therefore ruled no breach of Clauses 3.2 and 7.2 in that regard.

The Panel noted that the complainant provided two slides from the video in question, which he/she alleged were each examples of off-licence promotion. The Panel noted that the first slide included a summary of the cardiovascular trial outcomes including, *inter alia*, cardiovascular death or hospitalised heart failure; hospitalised heart failure; cardiovascular death, myocardial infarction or stroke. In this regard the complainant stated that most trial outcomes were not licensed indications and there was nothing present on the slides to make the audience aware that at best they are added benefits, rather than a reason to use the treatment. The second slide was titled 'Use of Canagliflozin in Clinical Practice for Patients With T2DM' followed by the following three statements: Canagliflozin as Treatment for Cardiovascular Disease; Canagliflozin as Treatment for Kidney Disease; and Canagliflozin as Treatment for Diabetes. Below these statements were the letter C, K and D. Letter C which was detailed as standing for cardiology and was associated with an image of a heart, K for kidney associated with an image of the kidneys and D for diabetes associated with an image of a pancreas.

The Panel noted that Clause 3.2 required that the promotion of a medicine must be in accordance with the terms of its marketing authorisation and must not be inconsistent with the particulars listed in its SPC. The Panel considered that it was not unacceptable for companies to promote the additional benefits that might be afforded from treatment with a particular medicine provided that those benefits were clearly set within the context of the licensed indication. The primary reason to prescribe must be made clear.

The Panel noted from Section 4.1 of the Invokana 100mg SPC that the licensed indication was:

> 'for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise
>
> - as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
> - in addition to other medicinal products for the treatment of diabetes
>
> For study results with respect to combination of therapies, effects on glycaemic control, cardiovascular and renal events, and the populations studied, see sections 4.4, 4.5 and 5.1.'

In Section 5.1 of the SPC it was stated, below a heading of 'Clinical efficacy and safety', that improvement in glycaemic control and reduction in cardiovascular and renal morbidity and mortality were integral parts of the treatment of type 2 diabetes.

The Panel noted Napp's submission that on 2 July 2020, the European Commission (EC) approved the extension of the indication of Invokana 100mg to include the renal outcomes data from the CREDENCE trial; a dedicated renal outcomes trial in patients with DKD and type 2 diabetes. The Panel further noted Napp's submission that the already approved indication 'treatment of patients with insufficiently controlled type 2 diabetes' was considered by the European Medicines Agency (EMA) to cover both the aim of the treatment, which was not limited to glycaemic control but covers as well other treatment goals including the prevention of worsening of diabetic complications and the target population (patients with DKD were not excluded from the current indication) and therefore it was considered that a separate indication for the treatment of diabetic kidney disease in section 4.1 of the SPC was not warranted. The

Panel noted that section 4.2 (Posology and method of administration) of the Invokana 100mg SPC stated under the heading 'Renal impairment' that, *inter alia*, 'for treatment of diabetic kidney disease as add on to standard of care (eg ACE-inhibitors or ARBs [angiotensin receptor blockers]), a dose of 100mg canagliflozin once daily should be used' and further included dose adjustment recommendations depending on the patient's eGFR or CrCl.

The Panel noted Napp's submission that renal protection information was included within the Invokana SPC following the outcome data from the CREDENCE trial and that the Invokana 100mg SPC now reflected the extended indication to treat diabetic kidney disease in type 2 diabetes patients as add on to standard of care (eg ACE inhibitors or angiotensin receptor blockers).

In the Panel's view, it was thus not necessarily unacceptable to refer to the renal benefits of Invokana in type 2 diabetes patients. Similarly, nor was it necessarily unacceptable to refer to its cardiovascular benefits; both appeared to be an integral part of the treatment of type 2 diabetes.

With regard to the off-licence promotion of Invokana's cardiovascular benefits, the Panel noted Napp's submission that the original 2013 licensed indication for Invokana (and other SGLT2 inhibitors) was focused on glycaemic (ie blood sugar) control. Following the publication of the phase 3 canagliflozin cardiovascular outcomes trial (CANVAS Program) in 2017 it was recognised that the treatment goals should also extend beyond blood glucose to address other significant diabetes complications, including cardiovascular protection. To reflect that, the licence was updated in 2018 by changing '…to improve glycaemic control' to '…for the treatment of adults with insufficiently controlled type 2 diabetes…' and as noted above, Section 5.1 of the Invokana SPC was referred to in Section 4.1 and stated, below a heading of 'Clinical efficacy and safety', that improvement in glycaemic control and reduction in cardiovascular and renal morbidity and mortality were integral parts of the treatment of type 2 diabetes.

The Panel considered that although the slide summarising the cardiovascular outcomes did not refer to type 2 diabetes, it noted Napp's submission that one of the objectives of session 2 'CREDENCE: bringing the data to life', in which the slide at issue appeared was to present the detailed study results including both the renal and cardiovascular endpoints from the study. Further the session began with describing the study and its design including that one of the key inclusion criteria was type 2 diabetes mellitus. The Panel noted that the slide in question followed a slide which discussed the incidence of hospitalised heart failure in clinical trials with SGLT2 inhibitors and the presenter stated that data from the CREDENCE trial showed that people with evidence of kidney damage in the presence of diabetes were not only at increased risk of developing kidney failure but also at the highest risk of developing heart failure too. The Panel further noted that at timepoint 29.27 minutes the speaker highlighted that the slide depicting hazard ratios represented a summary of the secondary cardiovascular outcomes from the CREDENCE study. In the Panel's view, viewers of the video would, therefore, view the cardiovascular outcomes on the slide in question in the context of type 2 diabetes. The slide referred to both the Invokana SPC and Mahaffey *et al* (2019)) for which the forest plots for those endpoints were included. The Panel did not consider that the complainant had established that the slide at issue promoted Invokana in a manner that was not in accordance with the terms of its marketing authorisation or was inconsistent with the SPC with regards to its cardiovascular benefits in type 2 diabetes patients as alleged; no breach of Clause 3.2 was ruled. Nor was the slide in the context of the overall presentation misleading in this regard and the Panel ruled no breach of Clause 7.2.

The complainant also referred to the final slide of the second session (timepoint 35:48) which was headed 'Use of Canagliflozin in Clinical Practice for Patients with [Type 2 Diabetes]'. The slide listed canagliflozin as treatment for cardiovascular disease, kidney disease and diabetes, in that order. Whilst the Panel was concerned that diabetes appeared last in the list and that below this list D(diabetes) with the associated pancreas image also appeared last following C(cardiology) and K(kidney) and the associated heart and kidney image respectively, the Panel noted that the title of the slide clearly referred to the use of canagliflozin in clinical practice for patients with type 2 diabetes. The Panel further noted that the presenter stated that Invokana had multiple benefits for patients with type 2 diabetes and especially those with evidence of kidney disease. It was stated that the CREDENCE trial had demonstrated that treatment with Invokana resulted in a reduced risk of major cardiovascular events and heart failure, a reduced risk of renal failure and transplantation and that it of course, had a glucose lowering effect. The Panel thus considered that it would be clear to viewers that the treatment of cardiovascular disease and kidney disease was in the context of the treatment of type 2 diabetes patients. The Panel, therefore, did not consider that the complainant had established that the slide at issue promoted Invokana in a manner that was not in accordance with the terms of its marketing authorisation or was inconsistent with its SPC with regards to its renal and cardiovascular benefits in type 2 diabetes patients as alleged; no breach of Clause 3.2 was ruled. Nor was the slide misleading in this regard and the Panel ruled no breach of Clause 7.2.

The Panel noted that the complainant alleged that the webpage which hosted the on demand video claimed that Invokana had a reno-protective effect which was off-licence. In that regard the complainant also referred to the slogan 'protect the kidney to protect the heart' which appeared as part of the presentation's title following 'CREDENCE: Type 2 Diabetes Management – A New Perspective'. The Panel considered that the information on the webpage in question regarding how Invokana might change the management of diabetic kidney disease in type 2 diabetes in the secondary care setting, based on the CREDENCE trial results and discussion of the renal outcomes in relation to the CREDENCE trial within the video itself, were clearly set within the context of the treatment of type 2 diabetes. The Panel considered that the complainant bore the burden of proof and had not established, on the balance of probabilities, that either the webpage or the associated video presentation promoted Invokana in a manner that was not in accordance with the terms of its marketing authorisation or was inconsistent with its SPC with regards to its renal benefits in type 2 diabetes patients as alleged and no breach of Clause 3.2 was ruled. Nor was the webpage or the presentation overall misleading in this regard and the Panel ruled no breach of Clause 7.2.

The Panel noted that the complainant provided a link to the webpage advertising the on demand video and then separately provided screenshots of and referred to the video presentation itself. The Panel considered both materials in relation to the complainant's general concern that not enough safety information had been given on the webpage including the use of Invokana in renal failure, in particular how the dose should be reduced or treatment not initiated in certain severities of renal failure given that the website purported a reno-protective effect of the product.

The Panel noted that whilst the webpage referred to the management of diabetic kidney disease in type 2 diabetes mellitus and included the strapline 'Protect the kidney to protect the heart', it did not include specific details with regard to treatment of patients with renal impairment with Invokana or provide any specific dosage instructions. The webpage encouraged readers to view the video to find out about what the Credence trial results might mean in practice. Further, the information was included within the Invokana prescribing information linked from the webpage and the agenda for session 3 referred to dosing considerations highlighting that it was

a topic that would be covered within the detail of the presentation. The Panel noted the secondary care audience and that Invokana (an SGLT2 inhibitor) had been in use since 2013 when the dosage in renal impairment was more restrictive that currently. The Panel noting it's comments above did not consider that, particularly given its purpose and content, the webpage was misleading as alleged. No breach of Clause 7.2 was ruled.

The Panel noted Napp's submission that in session 3 of the presentation which discussed how the CREDENCE data translated in a specialist clinical setting, the indication for Invokana was discussed in detail (starting at 42.50 minutes) and clearly highlighted the dose adjustments required for Invokana based on renal function as set out in its SPC. The Panel noted, however, that the slide displayed before the presentation began (ref UK/INV-20107p, July 2020), in addition to stating that Invokana was licenced for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise, also stated, with equal prominence and on a separate line, 'For treatment of diabetic kidney disease (DKD) in adults with [type 2 diabetes] as add-on to standard care, a dose of 100mg once-daily should be used. Please see Invokana SPC section 4.2 for details about dosing'.

The Panel considered that the statement about the treatment of diabetic kidney disease on this slide implied that all adult type 2 diabetes patients with diabetic kidney disease could be given 100mg Invokana which was not so. The Panel noted that a table of dose adjustment recommendations in Section 4.2 of the Invokana SPC showed that although patients with an estimated glomerular filtration rate (eGFR) of more than 30ml/min/1.73m^2 could be initiated on Invokana 100mg, those with an eGFR of less than 30ml/min/1.73m^2 could not be initiated on Invokana although if they had already started therapy at 100mg then it could be maintained. The Panel further noted that beneath the heading Renal impairment in Section 4.4 of the Invokana SPC, Special warnings and precautions for use, it stated 'The efficacy of canagliflozin for glycaemic control is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment (see section 4.2)'. It further stated that monitoring of renal function was recommended prior to initiation of canagliflozin and at least annually, thereafter (see Sections 4.2, 4.8, 5.1, and 5.2) and before initiation of concomitant medicines that might reduce renal function and periodically thereafter.

The Panel considered that the statement regarding the use of Invokana 100mg in diabetic kidney disease on the slide (ref UK/INV-20107p, July 2020) that displayed before the presentation began was thus misleading. That readers were referred to Section 4.2 of the SPC for details about dosing and a summary of the SPC dose adjustments based on renal function were highlighted towards the end of the presentation in session 3 (starting at 42.50 minutes) was insufficient to negate the immediate misleading impression that all adult type 2 diabetes patients with diabetic kidney disease could be given 100mg Invokana. A breach of Clause 7.2 was ruled.

The Panel noted that Clause 7.9 stated that information and claims about adverse reactions must reflect available evidence or be capable of substantiation by clinical experience. It must not be stated that a product had no adverse reactions, toxic hazards or risks of addiction or dependency. The word 'safe' must not be used without qualification. The Panel did not consider that the complainant had raised an allegation in that regard. Nonetheless, the Panel noted Napp's submission that Session 2 of the video presentation (starting at 17:41 minutes) discussed in detail the safety information of Invokana from the CREDENCE trial; the Panel

noted that this included adverse events experienced. The Panel therefore ruled no breach of Clause 7.9.

The Panel noted its comments and ruling above in relation to the misleading implication of the statement 'For treatment of diabetic kidney disease (DKD) in adults with [type 2 diabetes] as add-on to standard care, a dose of 100mg once-daily should be used' on the slide displayed before the presentation in question began without the inclusion of the relevant dosage adjustment requirements for renal impairment from section 4.2 of the SPC. The Panel considered that high standards had not been maintained and a breach of Clause 9.1 was ruled.

The Panel noted that examples of activities that were likely to be in breach of Clause 2 included prejudicing patient safety. The Panel noted the relevant sections of the SPC referred to above and considered that the claim put type 2 diabetes patients with diabetic kidney disease and an eGFR <30ml/min/1.73m^2 at risk of being initiated with Invokana 100mg when the SPC states that they should not be. The Panel considered that it was potentially prejudicial to patient safety and a breach of Clause 2 was ruled.

APPEAL FROM NAPP

Napp appealed the Panel's ruling of breaches of Clauses 7.2, 9.1 and 2.

Napp submitted that the ruling of a breach of Clause 7.2 was based on the slide displayed before the presentation began (ref UK/INV-20107p, July 2020), which stated that Invokana was licenced for the treatment of adults with insufficiently controlled type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise, and also stated on a separate line, 'For treatment of diabetic kidney disease (DKD) in adults with [type 2 diabetes] as add-on to standard care, a dose of 100mg once-daily should be used. Please see Invokana SPC section 4.2 for details about dosing'. While putting the information on this slide together, patient safety was the foremost consideration for Napp, with the intent behind the slide in question to ensure beyond doubt that the 300mg dose of canagliflozin should not be used to treat diabetic kidney disease (DKD) in adults with T2DM. Importantly, the statement around the 100mg dose was not an indication, was not meant as one and was simply a dosing recommendation to avoid confusion about the correct dose to be used in the treatment of DKD in adults with T2DM.

While approving the extension of the indication of Invokana 100mg (but not 300mg) to include the renal outcomes data from the Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial on 2 July 2020, the European Medical Agency (EMA) were of the view that the already approved indication 'treatment of patients with insufficiently controlled type 2 diabetes' was considered to cover both the aim of the treatment, which was not limited to glycaemic control but covered other treatment goals as well including the prevention of worsening of diabetic complications and the target population (patients with DKD were not excluded from the current indication). It was considered that a separate indication for the treatment of diabetic kidney disease in section 4.1 of the SPC was not warranted.

Hence, Napp submitted that treatment of T2DM could be three-fold as below and associated dosage of canagliflozin for treating these conditions were also indicated for clarification purposes:

1. Treatment of HbA1c – indicated canagliflozin dose: 100mg or 300mg

2. Treatment of ONLY CV Risk in T2DM patients (with stable HbA1c) – indicated canagliflozin dose: 100mg or 300mg
3. Treatment of ONLY DKD in T2DM patients (with stable HbA1c) – indicated canagliflozin dose: 100mg only

Napp submitted that all of the bullet points above were listed under therapeutic indications within the Invokana 100mg SPC, section 4.1 and further elaborated in sections 4.2, 4.4, 4.5, 5.1. Napp's sole intention of highlighting the use of 100mg for T2DM patients with DKD on the title slide of the webinar was to make sure there was no confusion by the health professionals about what was the correct dose of canagliflozin that should be used in T2DM patients with DKD which was the topic of focus for the webinar in question, to prevent inadvertent use of the 300mg dose in those patients and therefore to protect patient safety.

Napp submitted that the wording, taken from the SPC, was presented on the title slide of the webinar, to ensure delegates would not assume the 300mg dose could be used in DKD (as they could indeed do for HbA1c reductions and prevention of CV events). However, that did not and should not imply all patients with T2DM and DKD could be treated with Invokana 100mg. As demonstrated in innumerable examples of promotional materials developed by pharmaceutical companies and not found in breach by the Panel, it was not a requirement to list out every type of patient or subgroup that were excluded from the license wording in every instance the indication or dosing was listed in promotional material. Indeed, there were no medicines available on the UK market that were suitable for all patients that were represented by the wording of the licensed indication. This did not mean simply stating the licence alone was tantamount to implying all such patients could be treated with the medicine. To reiterate, the treatment of DKD in T2DM was a licensed indication granted by EMA, and the associated dose for the indication was 100mg daily. To suggest that highlighting the correct dose was tantamount to suggesting all patients were eligible was counter to any previous rulings made by the Panel. Napp submitted that it was not aware of any rulings made by the Panel where companies had displayed a licensed indication and dose, and the Panel had ruled that this was misleading and a danger to patient safety on the basis that this would imply all such patients (as per the wording of the indication) were eligible. Furthermore, Napp specifically referred delegates to the relevant section of the SPC for further information on dosing. This, as well as the discussion of the indication and use of Invokana in different patient groups in detail during the webinar (UK/INV-20107ab, starting at 42.50 minutes), clearly highlighted the dose adjustments required for Invokana based on patients' renal function were appropriate and in-line with Napp's intention to protect patient safety. The prescribing information was also provided at the end of the presentation once again (UK/INV-20107ab, starting at 01.05.38).

Napp stressed its diligence about patient safety, the aim while specifically mentioning the use of 100mg dose of canagliflozin for T2DM patients with DKD on the title slide of the webinar was to make it clear that if health professionals aimed to treat options 1 and 2 above in T2DM patients, then 300mg of canagliflozin could be used according to the SPC, whereas the patients that fell under bullet point number three above (DKD patients) should not be treated with 300mg of canagliflozin according to the SPC. Napp hoped that the Appeal Board would agree that this practice aimed to preserve patient safety and ensured the correct use of canagliflozin.

Napp submitted that it aligned with the Panel's description of Clause 2 that activities or materials must never be such as to bring discredit upon or reduce confidence in the pharmaceutical industry and that rulings of Clause 2 should be reserved for cases of particular censure. In such cases, the activity or material in question must be beyond dispute in regard to their breach of

Clause 2, something that this case was not and so Napp requested caution when ruling a Clause 2 when the nature of the proposed breach did not merit such a sanction.

In conclusion, Napp submitted that it had explained how it had maintained high standards (Clause 9.1) and made clear why it refuted a breach of Clause 7.2. Napp submitted that it had upheld the highest standards and had not brought discredit upon, or reduced confidence in the pharmaceutical industry, and therefore refuted a breach of Clause 9.1 and Clause 2.

COMMENTS FROM COMPLAINANT

There were no comments from the complainant.

APPEAL BOARD RULING

The Appeal Board noted that the slide at issue (ref UK/INV-20107p, July 2020) stated:

> '***Invokana***® (canagliflozin) is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise.
>
> For treatment of diabetic kidney disease (DKD) in adults with T2DM as add-on to standard of care, a dose of 100 mg once-daily should be used. Please see Invokana SmPC section 4.2 for details about dosing.
>
> Prescribing information for ***Invokana*** is included at the end of this presentation.'

The Appeal Board noted that slide was shown for several seconds before the main presentation of over 1 hour and five-minutes duration began. Later in the presentation (starting at 42.50 minutes) details from Section 4.2 of the SPC about dose adjustment recommendations based on renal function were given.

The Appeal Board noted that a table of dose adjustment recommendations in Section 4.2 of the Invokana SPC showed that although patients with an estimated glomerular filtration rate (eGFR) of more than 30ml/min/1.73m^2 could be initiated on Invokana 100mg, those with an eGFR of less than 30ml/min/1.73m^2 should not be initiated on Invokana although if they were already taking Invokana then it could be continued at 100mg.

The Appeal Board noted from the representatives from Napp that the slide at issue was no longer in use and in its place the company now included the full wording from Section 4.1 of the SPC. Section 4 was headed 'Clinical particulars' and Section 4.1 was headed 'Therapeutic indications'. The Napp representatives stated that the slides were never available for download, they could only be viewed in the video.

The Appeal Board considered that when treating diabetes patients with renal impairment health professionals would be especially cautious and were likely to consult the SPC before prescribing. In that regard the Appeal Board noted the reference on the slide at issue to prescribing information being available at the end of the presentation. In addition, the slide included '…Please see Invokana SmPC section 4.2 for details about dosing'. The Appeal Board considered that whilst Napp had chosen to refer prescribers to Section 4.2 on dosing it might have been clearer, given the topic of the presentation, to include a statement summarising the dose adjustment recommendations according to eGFR from Section 4.2 of the SPC. However,

the Appeal Board noted that the slide only appeared briefly and that later in the presentation a summary of the SPC dose adjustments based on renal function and that certain patients could continue on Invokana but should not be initiated on the medicine was included. Taking all the circumstances into account the Appeal Board considered that in the context of the video, the slide at issue did not misleadingly imply that all adult type 2 diabetes patients with diabetic kidney disease could be given 100mg Invokana. The Appeal Board ruled no breach of Clause 7.2. Consequently, the Appeal Board ruled no breach of Clauses 9.1 and 2. The appeal on all points was successful.

Complaint received **19 January 2021**

Case completed **1 October 2021**