CASE AUTH/2836/4/16

ASTRAZENECA v JANSSEN

Promotion of Invokana

AstraZeneca UK complained about two leavepieces and a journal advertisement for Invokana (canagliflozin) issued by Janssen-Cilag.

Invokana was a sodium glucose co-transporter 2 inhibitor (SGLT2i) indicated to improve glycaemic control in adult type 2 diabetics: as monotherapy when diet and exercise did not provide adequate glycaemic control in those for whom using metformin was inappropriate and as add-on therapy with other glucose lowering medicines, including insulin, when these together with diet and exercise did not provide adequate glycaemic control.

The front page of the October 2015 leavepiece stated 'Invokana 100mg and 300mg efficacy and flexibility* at a single price'. This claim was referenced to Lavalle-González *et al* (2013), Schernthaner *et al* (2013) and the Invokana prescribing information. A footnote at the bottom of the page stated '*The recommended starting dose of Invokana is 100mg once daily. In patients tolerating Invokana 100mg once daily, who have an eGFR [estimated glomerular filtration rate] ≥60mL/min/1.73m^2 and need tighter glycaemic control, the dose can be increased to 300mg'.

Page 2 included comparisons between Invokana 100mg and 300mg and baseline and Invokana 100mg and 300mg and sitagliptin (Merck Sharp & Dohme's product Janumet). The comparison with sitagliptin was referenced to Lavalle-González *et al*. The claim on page 2 'The only SGLT2i to offer reductions in HbA1c greater than 1% across four clinical trials' was referenced to Schernthaner *et al*, Stenlöf *et al* (2013), Forst *et al* (2014) and Wilding *et al* (2013). Page 3 included claims 'Invokana can be used in combination with other anti-diabetic agents' referenced to the Invokana summary of product characteristics (SPC) and the patient information leaflet.

The claim on page 3 'Invokana is generally well-tolerated with a low risk of hypoglycaemia †' was referenced to Lavalle-González *et al*, and the Invokana SPC. The explanation for † appeared in very small print, amongst over 6 lines of equally small text, at the bottom of the page; the incidence of hypoglycaemia was stated (approximately 4% among treatment groups including placebo) when used as monotherapy or as add-on to metformin. Hypoglycaemia was the most commonly reported adverse reaction when Invokana was used as add-on therapy with insulin or a sulphonylurea. When Invokana was used with insulin or an insulin secretagogue (eg sulphonylurea) a lower dose of insulin secretagogue might be considered to reduce the risk of hypoglycaemia.

The claim 'Invokana 100mg can continue to be prescribed in patients who develop an eGFR 45-60mL/min/1.73m2‡4' was referenced to the SPC. Reference 2 was Schernthaner *et al* but it was not clear whether 2 referred to reference 2 or to m^2. The explanation for ‡, again in very small print at the bottom of the page, stated that the Invokana dose should be adjusted to or maintained at 100mg for patients developing moderate renal impairment (eGFR 45-60mL/min/1.73m^2). If renal function fell persistently below eGFR 45mL/min/1.73m^2 or CrCl <45mL/min [creatinine clearance] Invokana treatment should be discontinued.

The front page of the January 2016 leavepiece stated 'The only SGLT2 inhibitor with a proven efficacy profile vs sitagliptin in dual therapy was also referenced to Lavalle-González'.

AstraZeneca noted that Section 4.2 of the Invokana SPC stated that 'The recommended starting dose of canagliflozin is 100mg once daily. In patients tolerating canagliflozin 100mg once daily who have an eGFR ≥60 mL/min/1.73m^2 or CrCl ≥60 mL/min and need tighter glycaemic control, the dose can be increased to 300mg once daily orally'.

AstraZeneca alleged that promotional claims regarding the 300mg dose of Invokana that were based upon Lavalle-González *et al*, Schernthaner *et al*, Stenlöf *et al*, Forst *et al* and Wilding *et al* were misleading in breach of the Code. For example, in the October 2015 leavepiece claims were made about the efficacy of the 300mg dose, as well as its comparative efficacy vs sitagliptin. The studies used to support these claims, however, used 300mg as a starting does in SGLT2 inhibitor-naïve patients, ie in a manner inconsistent with the posology in the SPC. AstraZeneca alleged that use of these studies to substantiate claims for the 300mg dose was thus misleading. Further, comparisons to sitagliptin which referenced the above studies were misleading.

AstraZeneca stated that Janssen acknowledged during inter-company dialogue that no evidence existed to substantiate claims for the 300mg dose where Invokana was given in a manner consistent with the SPC. AstraZeneca alleged this breached the Code and demonstrated a failure to maintain high standards.

The detailed response from Janssen is given below.

The Panel noted that some of the studies cited in the October 2015 leavepiece used Invokana 300mg as the starting dose. This was inconsistent with the indication in the SPC that the recommended starting dose was 100mg. In certain patients the dose could be increased to 300mg.

The Panel noted Janssen's submission that differences in the dosing regimen during clinical development and the dosing set out in the SPC were common in conditions when patients might require different doses to manage their condition. The Panel also noted that there was no recommended

time period in the SPC for the 100mg dose before a patient could have a dose increase to 300mg.

The Panel noted Janssen's submission that some of SPC data were from studies in which treatment was started at 300mg rather than 100mg and increasing to 300mg as required. Section 4.8, Undesirable effects stated that the safety evaluation included patients treated with 100mg and 300mg Invokana who took part in nine phase 3 clinical studies. Section 5.1, Pharmacodynamic properties, stated beneath the heading 'Clinical efficacy and safety' that 10,285 type 2 diabetics participated in nine double-blind controlled clinical efficacy and safety studies conducted to evaluate the effects of Invokana on glycaemic control. It appeared to the Panel that the studies in Sections 4.8 and 5.1 were the same.

The Panel considered that data in the SPC could be used in promotional material provided it was presented in context. The Panel noted that Table 2 in Section 5.1 compared efficacy results from placebo-controlled clinical studies at 26 weeks (18 weeks when added to insulin therapy). It included a comparison of Invokana 100mg and 300mg as an add-on to metformin at 26 weeks and included data on reductions in HbA1c (-0.94 from baseline (7.95)) for 300mg dose and in weight (85.4kg at baseline reduced by 4.2% for 300mg dose). This section of the SPC also stated that in placebo-controlled studies Invokana 100mg and 300mg resulted in mean reductions in systolic blood pressure of -3.9mmHg and 5.3mmHg respectively compared to placebo. This section of the SPC did not give any details about the starting dose of Invokana ie whether it was 100mg or 300mg or whether there were any differences resulting from starting with 300mg compared to 100mg Invokana. Neither was this detail included in the leavepiece. The leavepiece gave results at 52 weeks. The SPC only included data at 26 weeks.

The Panel also noted AstraZeneca's submission that Janssen acknowledged there was no published evidence regarding whether there was a clinically meaningful difference in the observed efficacy of Invokana 300mg whether it was initiated at the start of therapy or following the 100mg dose.

The efficacy results from active-controlled clinical studies were given in Table 3 of the SPC and included a comparison with sitagliptin as triple therapy (with metformin and sulphonylurea) at 52 weeks. There was no data in the SPC setting out the comparison in the leavepiece ie comparing sitagliptin and Invokana 100mg and 300mg as add-on therapy to metformin alone. The SPC did not include comparisons of Invokana and sitagliptin in relation to their effects on systolic blood pressure.

The Panel noted that the claims in the leavepiece comparing sitagliptin and Invokana 300mg as add-on to metformin were based on the registration studies not all of which were included in detail in the SPC including in Table 3.

The Panel considered it was very difficult to understand the basis of the comparison on page 2 of the leavepiece as the claims were followed by * and the explanation was provided within over 6 lines of small type at the foot of page 3. It was not clear on page 2 that the recommended starting dose was 100mg Invokana.

The Panel noted AstraZeneca's allegation that it was a breach of the Code to use references from studies starting at 300mg Invokana to support claims in the leavepiece. The Panel noted Janssen's submission that the data in the leavepiece were from the pivotal registration studies, reviewed by the Committee for Medicinal Products for Human Use (CHMP) as part of the marketing authorization and the SPC was based on these data. The Panel noted Janssen's submission that the SPC included data where treatment started with 300mg Invokana rather than being increased from 100mg. The Panel therefore considered on the very narrow grounds of the complaint that it was not necessarily inconsistent with the SPC to cite studies with a starting dose of Invokana of 300mg in the leavepiece as alleged. Similarly, the use of these references to substantiate claims for 300mg Invokana was not necessarily misleading as alleged. There was no complaint that the detailed data in the leavepiece was inconsistent with the detailed data in the SPC. No breach of the Code was ruled which was upheld on appeal by AstraZeneca.

With regard to the comparison with sitagliptin the Panel noted its ruling above and decided that was also relevant here. The Panel ruled no breach of the Code which was upheld on appeal by AstraZeneca.

The Panel noted that none of the five studies cited on page 3 for the Invokana 300mg dose claims started patients on 100mg and increased up to 300mg Invokana as stated in the indication section of the SPC. AstraZeneca alleged that there was no data to substantiate claims for the 300mg dose when given in a manner consistent with the SPC. The Panel noted its comments above regarding the SPC which included Invokana 300mg data as a starting dose. It decided that, on balance, in general the claims could be substantiated by the studies cited. However, the Panel noted page 3 included a claim that Invokana reduced HbA1c greater than 1% across four clinical trials. This was not so as at week 52 in Wilding *et al* (one of the four cited studies) 300mg Invokana reduced HbA1c by 0.96%. Thus the Panel ruled a breach of the Code.

In the circumstances, the Panel did not consider that there had been a failure to maintain high standards. No breach of the Code was ruled which was upheld on appeal by AstraZeneca.

The journal advertisement, dated September 2015, was headed 'Invokana 100mg and 300mg efficacy and flexibility* at a single price'. A footnote in very small print at the bottom of the page stated '*The recommended starting dose of Invokana is 100mg once daily. In patients tolerating Invokana 100mg once daily, who have a eGFR ≥60mL/min/1.73m^2 and need tighter glycaemic control, the dose can be increased to 300mg'.

The heading was followed by hanging signs representing cost, reductions in HbA1c, kg and mmHg. There were then sections headed 'Invokana 100mg' and 'Invokana 300mg'. The Invokana 100mg section included favourable comparison in HbA1c, weight and blood pressure reductions vs sitagliptin in dual therapy as add-on therapy to metformin referenced to Lavalle-González *et al*. The Invokana 300mg section included favourable comparison with HbA1c, weight and blood pressure reductions with sitagliptin in dual and triple therapy as add-on to metformin and as add-on to metformin and sulphonylurea. Each section contained comparisons between the Invokana dose and sitagliptin.

The same claim appeared on the front page of the October 2015 leavepiece which was also followed by the hanging signs.

AstraZeneca alleged that 'flexibility' breached the Code and was inconsistent with the SPC. The journal advertisement used 'flexibility' in its title and gave equal prominence to the 100mg and 300mg doses implying that 300mg dose could be initiated and/or administered interchangeably with 100mg. This impression was not negated by the small footnote near the bottom of the page that 'The recommended starting dose of INVOKANA is 100mg once-daily. In patients tolerating INVOKANA 100mg once-daily, who have an eGFR ≥60ml/min/1.73m^2 and need tighter glycaemic control, the dose can be increased to 300mg once-daily'.

AstraZeneca stated that the same was true for the October 2015 leavepiece.

AstraZeneca alleged that 'flexibility' constituted promotion outside the scope of the marketing authorization; the claim was misleading and as it was not possible to substantiate claims around 'flexibility' this was a failure to maintain high standards.

The Panel considered that the claim in the advertisement ('Invokana 100mg and 300mg efficacy and flexibility at a single price)' did not make it sufficiently clear where each dose fitted in to the treatment pathway. The Panel did not accept Janssen's submission that the claim was qualified by the use of the asterisk and its explanation regarding the recommended starting dose. It was a principle under the Code that claims should not be qualified by footnotes, they should be capable of standing alone as regards accuracy etc.

The Invokana SPC was clear that the recommended starting dose was 100mg once daily. There was no indication in the posology section as to how long the 100mg starting dose should be used before increasing it to 300mg in appropriate patients.

The Panel considered that the claim 'flexibility' could be read as relating to the starting dose and not as submitted by Janssen that some patients started out on 100mg could increase their dose to 300mg and this would not mean an increase in cost. The Panel considered that the claim was misleading and inconsistent with the SPC. The Panel ruled breaches of the Code. With regard to substantiation the Panel accepted that there was data relating to both doses and in relation to starting with the 300mg dose as referred to above. The Panel thus ruled no breach of the Code which was upheld on appeal by AstraZeneca.

On balance, the Panel did not consider that the claim meant that high standards had not been maintained and no breach of the Code was ruled which was upheld on appeal by AstraZeneca.

AstraZeneca alleged that overall the claims at issue represented a deliberate attempt to misrepresent the facts and noted that the European Public Assessment Report for Invokana twice stated that patients should always be initiated on the 100mg dose for safety reasons.

AstraZeneca therefore alleged that use of the word 'flexibility' had the potential to compromise patient safety and to bring discredit to, and reduce confidence in, the pharmaceutical industry in breach of Clause 2.

The Panel noted its rulings above. It did not consider that the use of the word 'flexibility' compromised patient safety such that Janssen had brought discredit upon or reduced confidence in the pharmaceutical industry. The Panel therefore ruled no breach of Clause 2 of the Code which was upheld on appeal by AstraZeneca.

AstraZeneca UK Limited complained about the promotion of Invokana (canagliflozin) by Janssen-Cilag Ltd. The materials at issue were two leavepieces (refs October 2015 PHGB/VOK/0815/0020 and January 2016 PHGB/VOK/0815/0020(1)) and a journal advertisement (ref September 2015 PHGB/VOC/0815/0018).

Invokana was a sodium glucose co-transporter 2 inhibitor (SGLT2i) indicated for the treatment of type 2 diabetes mellitus in adults to improve glycaemic control: as monotherapy when diet and exercise did not provide adequate glycaemic control in patients for whom using metformin was inappropriate due to intolerance or contraindications and as add-on therapy with other glucose lowering medicinal products, including insulin, when these together with diet and exercise did not provide adequate glycaemic control.

1 Starting dose

The front page of the October 2015 leavepiece stated 'Invokana 100mg and 300mg efficacy and flexibility* at a single price'. This claim was referenced to Lavalle-González *et al* (2013), Schernthaner *et al* (2013) and the Invokana prescribing information. A footnote at the bottom of the page stated '*The recommended starting dose of Invokana is 100mg once daily. In patients tolerating Invokana 100mg once daily, who have an eGFR [estimated glomerular filtration rate] ≥60mL/min/1.73m^2 and need tighter glycaemic control, the dose can be increased to 300mg'.

Page 2 included comparisons between Invokana 100mg and 300mg and baseline and Invokana 100mg and 300mg and sitagliptin (Merck Sharp & Dohme's

product Janumet). The comparison with sitagliptin was referenced to Lavalle-González *et al*. The claim on page 2 'The only SGLT2i to offer reductions in HbA1c greater than 1% across four clinical trials' was referenced to Schernthaner *et al*, Stenlöf *et al* (2013), Forst *et al* (2014) and Wilding *et al* (2013). Page 3 included claims 'Invokana can be used in combination with other anti-diabetic agents' referenced to the Invokana summary of product characteristics (SPC) and the patient information leaflet.

The claim on page 3 'Invokana is generally well-tolerated with a low risk of hypoglycaemia †' was referenced to Lavalle-González *et al*, and the Invokana SPC. The explanation for † appeared in very small print, amongst over 6 lines of equally small text, at the bottom of the page; the incidence of hypoglycaemia was stated (approximately 4% among treatment groups including placebo) when used as monotherapy or as add-on to metformin. Hypoglycaemia was the most commonly reported adverse reaction when Invokana was used as add-on therapy with insulin or a sulphonylurea. When Invokana was used with insulin or an insulin secretagogue (eg sulphonylurea) a lower dose of insulin secretagogue might be considered to reduce the risk of hypoglycaemia.

The claim 'Invokana 100mg can continue to be prescribed in patients who develop an eGFR 45-60mL/min/1.73m^2‡4' was referenced to the SPC. Reference 2 was Schernthaner *et al* but it was not clear whether 2 referred to reference 2 or to m^2. The explanation for ‡, again in very small print at the bottom of the page, stated that the Invokana dose should be adjusted to or maintained at 100mg for patients developing moderate renal impairment (eGFR 45-60mL/min/1.73m^2). If renal function fell persistently below eGFR 45mL/min/1.73m^2 or CrCl <45mL/min [creatinine clearance] Invokana treatment should be discontinued.

The front page of the January 2016 leavepiece stated 'The only SGLT2 inhibitor with a proven efficacy profile vs sitagliptin in dual therapy was also referenced to Lavalle-González'.

COMPLAINT

AstraZeneca noted that Section 4.2 of the Invokana SPC stated:

> 'The recommended starting dose of canagliflozin is 100mg once daily. In patients tolerating canagliflozin 100mg once daily who have an eGFR ≥60mL/min/1.73m^2 or CrCl ≥60mL/min and need tighter glycaemic control, the dose can be increased to 300mg once daily orally.'

AstraZeneca alleged that promotional claims regarding the 300mg dose of Invokana that were based upon the studies referenced, Lavalle-González *et al*, Schernthaner *et al*, Stenlöf *et al*, Forst *et al* and Wilding *et al* were misleading in breach of the Code. For example, in the October 2015 leavepiece claims about the efficacy of the 300mg dose and its comparative efficacy vs sitagliptin were studies in which the 300mg dose was indicated in SGLT2 inhibitor-naïve patients, ie in a manner inconsistent with the posology in the SPC. AstraZeneca alleged that use of these studies to substantiate claims for the 300mg dose was thus misleading in breach of Clause 7.2. Further, comparisons with sitagliptin which referenced the above studies breached Clause 7.3. While the October 2015 leavepiece had been withdrawn, similar claims were made in more recent promotional items such as the January 2016 leavepiece.

AstraZeneca referred to Janssen's notes on the inter-company telephone call on 16 March 2016, which stated:

> '[T]here was no published evidence to suggest that there either is or is not a clinical meaningful difference in the observed efficacy of canagliflozin 300mg whether it was initiated at the start or following the titration posology stated in the SPC.'

AstraZeneca alleged that Janssen therefore acknowledged that no evidence existed to substantiate claims for the 300mg dose where Invokana was given in a manner consistent with the SPC. AstraZeneca alleged this breached Clause 7.4 and demonstrated a failure to maintain high standards in breach of Clause 9.1.

RESPONSE

Janssen stated that there were two approved doses 100mg and 300mg, and the posology section of the SPC stated:

> 'The recommended starting dose of canagliflozin is 100mg once daily. In patients tolerating canagliflozin 100mg once daily who have an eGRR ≥ 60mL/min/1.73m^2 or CrCl ≥ 60mL/min and need tighter glycaemic control, the dose can be increased to 300mg once daily orally.'

Invokana 100mg and 300mg had been the same list price since August 2015. Efficacy and tolerability data were presented in promotional materials for the 100mg and 300mg doses and it was always made clear within materials that patients should be started on Invokana 100mg.

Janssen refuted AstraZeneca's allegations that claims around 300mg Invokana could not be substantiated and it was misleading to promote results from the pivotal registration studies using Invokana 300mg because of the difference between the Invokana dosing schedule in the clinical development programme and the SPC posology (ie initiate Invokana on 100mg and increase to 300mg if tighter glycaemic control was needed). Janssen submitted that the claims were based on the marketing authorization for Invokana on the approved patient population (adults with type 2 diabetes). The claims could be substantiated by both the provision of the SPC and published papers. Janssen did not agree that it had not maintained high standards (Clause 9.1).

Janssen submitted that claims in relation to 300mg Invokana were referenced to published data from the studies in the extensive clinical development

programme. These studies formed part of the submission to the regulatory authorities and were in the marketing authorizations for both doses. The SPC included data from nine phase 3 clinical studies, eight of which had the doses of 100mg and 300mg Invokana. Results from these studies demonstrated the safety and efficacy profiles of the maintenance doses of 100mg, 300mg Invokana and comparator(s) during the clinical studies and at the study endpoints. The details in Section 4, Clinical particulars, of the SPC were based on the data from these clinical studies.

Janssen stated that in nine phase 3 studies Invokana was studied as an initiation dose and maintenance dose of 100mg or 300mg compared with placebo or active control: as monotherapy and add-on therapy with glucose-lowering medicines including insulin, when diet and exercise alone did not provide adequate glycaemic control. Efficacy results of these studies were described in Section 5.1, Pharmacodynamic properties, and summarised in Tables 2 (Efficacy results from placebo-controlled clinical studies) and 3 (Efficacy results from active-controlled clinical studies) in the SPC. Adverse event information from these studies were assessed and formed part of the overall safety assessment of both doses of Invokana described in Section 4.8, Undesirable effects, of the SPC, which was summarised in Table 1 (Tabulated list of adverse reactions (MedDRA) [Medical Dictionary of Regulatory Activities] from placebo-controlled studies and from postmarketing experience). All of these studies, except the ongoing cardiovascular safety study, had been published.

Janssen submitted that in line with accepted clinical practice, the posology in the SPC recommended that patients started at the lowest effective dose and then increased if the patient tolerated the 100mg dose and additional efficacy was required. This posology had been determined from the submitted package outlined above.

Janssen submitted that it took patient safety extremely seriously and recognised that in promotional material it needed clarity that the licence recommended initiation on Invokana 100mg with patients increased to 300mg where appropriate. Thus, Janssen had always made clear the licensed posology in promotional materials.

Janssen noted that differences in dosing regimen during clinical development and recommended posology after marketing approvals were common in conditions where patients might require different doses to manage their condition and in order to reach individual treatment goals, eg anti-hyperglycaemic agents, antihypertensive and lipid lowering agents. AstraZeneca, as well as others carried licences for their medicines where similar decisions had been made by the regulatory authorities on data packages where no 'step up' data was submitted.

The clinical study designs, the results in conjunction with the SPC were reviewed by the Committee for Human Medicinal Products (CHMP) and authorized by the European Commission. The CHMP had access to full data from the clinical programme and approved the posology in the SPC based on the information provided. Janssen submitted that the experience and access to data by this committee was more relevant than the experience and access to data available to AstraZeneca. Indeed, AstraZeneca's assertion that Janssen could not use the pivotal registration studies that formed the basis of the marketing authorization to substantiate claims for the 300mg dose was tantamount to saying it could not promote 300mg Invokana.

In summary, Janssen submitted that it had clearly presented information on 100mg Invokana, 300mg Invokana, placebo and/or active control (if included in the study referenced) and the posology for use. The claims for the efficacy of Invokana 300mg were in line with the SPC and could be substantiated. Based on the evidence above, Janssen refuted the allegations that claims for Invokana 300mg were inaccurate, unbalanced, unfair, not objective, ambiguous, outdated, misleading, not capable for substantiation and that Janssen had not maintained high standards. Thus, Janssen denied breaches of Clauses 7.2, 7.3, 7.4 and 9.1.

PANEL RULING

The Panel noted that some of the studies cited in the October 2015 leavepiece used Invokana 300mg as the starting dose. This was inconsistent with the indication in the SPC that the recommended starting dose was 100mg. In certain patients the dose could be increased to 300mg.

The Panel noted Janssen's submission that differences in the dosing regimen during clinical development and the dosing set out in the SPC were common in conditions when patients might require different doses to manage their condition. The Panel also noted that there was no recommended time period in the SPC for the 100mg dose before a patient could have a dose increase to 300mg.

The Panel noted Janssen's submission that some of the data included in the SPC were from studies in which treatment was started at 300mg rather than 100mg and increasing the dose as required. Section 4.8, Undesirable effects, stated that the safety evaluation included patients treated with 100mg and 300mg Invokana who took part in nine phase 3 clinical studies. Section 5.1, Pharmacodynamic properties, stated beneath the heading 'Clinical efficacy and safety' that 10,285 type 2 diabetics participated in nine double-blind, controlled clinical efficacy and safety studies conducted to evaluate the effects of Invokana on glycaemic control. It appeared to the Panel that the studies in Sections 4.8 and 5.1 were the same.

The Panel considered that if the data was in the SPC it could, of course, be used in promotional material provided such data was presented in context. The Panel noted that Table 2 in Section 5.1 compared efficacy results from placebo-controlled clinical studies at 26 weeks (18 weeks when added to insulin therapy). It included a comparison of Invokana 100mg and 300mg as an add-on to metformin at

26 weeks and included data on reductions in HbA1c (-0.94 from baseline (7.95)) for 300mg dose and in weight (85.4kg at baseline reduced by 4.2% for 300mg dose). This section of the SPC also stated that in placebo-controlled studies Invokana 100mg and 300mg resulted in mean reductions in systolic blood pressure of -3.9mmHg and 5.3mmHg respectively compared to placebo. This section of the SPC did not give any details about the starting dose of Invokana ie whether it was 100mg or 300mg or whether there were any differences resulting from starting with 300mg compared to 100mg Invokana. Neither was this detail included in the leavepiece. The leavepiece gave results at 52 weeks. The SPC only included data at 26 weeks.

The Panel also noted AstraZeneca's submission that Janssen acknowledged there was no published evidence regarding whether there was a clinically meaningful difference in the observed efficacy of Invokana 300mg whether it was initiated at the start of therapy or following the 100mg dose.

The efficacy results from active-controlled clinical studies were given in Table 3 of the SPC and included a comparison with sitagliptin as triple therapy (with metformin and sulphonylurea) at 52 weeks. There was no data in the SPC setting out the comparison in the leavepiece ie comparing sitagliptin and Invokana 100mg and 300mg as add-on therapy to metformin alone. The SPC did not include comparisons of Invokana and sitagliptin in relation to their effects on systolic blood pressure.

The Panel noted that the claims in the leavepiece comparing sitagliptin and Invokana 300mg as add-on to metformin were based on the registration studies not all of which were included in detail in the SPC including in Table 3.

The Panel considered it was very difficult to understand the basis of the comparison on page 2 of the leavepiece as the claims were followed by * and the explanation was provided within over 6 lines of small type at the foot of page 3. It was not clear on page 2 that the recommended starting dose was 100mg Invokana.

The Panel noted AstraZeneca's allegation that it was a breach of the Code to use references from studies starting at 300mg Invokana to support claims in the leavepiece. The Panel noted Janssen's submission that the data in the leavepiece were from the pivotal registration studies, reviewed by the CHMP as part of the marketing authorization and the SPC was based on these data. The Panel noted Janssen's submission that the SPC included data where treatment started with 300mg Invokana rather than being increased from 100mg. The Panel therefore considered on the very narrow grounds of the complaint that it was not necessarily inconsistent with the SPC to use studies with a starting dose of Invokana of 300mg as references to claims in the leavepiece as alleged. Similarly, the use of these references to substantiate claims for 300mg Invokana was not necessarily misleading as alleged. There was no complaint that the detailed data in the leavepiece was inconsistent with the detailed data in the SPC. No breach of Clause 7.2 was ruled. This ruling was appealed.

With regard to the comparison with sitagliptin the Panel noted its ruling above and decided that was also relevant here. The Panel ruled no breach of Clause 7.3. This ruling was appealed.

The Panel noted that none of the five studies cited on page 3 for the Invokana 300mg dose claims started patients on 100mg and increased the dose to 300mg Invokana as stated in the indication section of the SPC. AstraZeneca alleged that there was no data to substantiate claims for the 300mg dose when given in a manner consistent with the SPC. The Panel noted its comments above regarding the SPC which included Invokana 300mg data as a starting dose. It decided that, on balance, in general the claims were capable of substantiation by the studies cited. However, the Panel noted page 3 included a claim that Invokana reduced HbA1c greater than 1% across four clinical trials. This was not so as at week 52 in Wilding *et al* (one of the four cited studies) 300mg Invokana reduced HbA1c by 0.96%. Thus the Panel ruled a breach of Clause 7.4 of the Code.

In the circumstances, the Panel did not consider that there had been a failure to maintain high standards. No breach of Clause 9.1 was ruled. This ruling was appealed.

APPEAL BY ASTRAZENECA

AstraZeneca noted that Section 4.2 of the Invokana SPC stated:

> 'The recommended starting dose of canagliflozin is 100mg once daily. In patients tolerating canagliflozin 100mg once daily who have an eGFR≥60mL/min/1.73m^2 or CrCl≥60mL/min and need tighter glycaemic control, the dose can be increased to 300mg once daily orally.'

AstraZeneca stated that as noted by the Panel, it was possible to use data from all sections of the SPC provided that it was presented in context. For example in Cases AUTH/2506/5/12 and AUTH/2507/5/12, the Panel considered that data in sections other than 4.2 of the SPC might be used in promotional material but such references should be secondary to the statement in Section 4.2 in relation to the recommended posology.

AstraZeneca alleged that efficacy claims for the 300mg dose implied that such results could be expected when the medicine was initiated as per the SPC. This was not the case given that the substantiation provided for the comparisons, Lavalle-Gonzalez *et al*, Schernthaner *et al*, Stenlöf *et al*, Forst *et al* and Wilding *et al*, were studies in which Invokana was started at a dose of 300mg. This was misleading, in breach of Clause 7.2, as it was not possible to state on the basis of these studies, what results could be expected when Invokana was used in line with the licensed posology.

AstraZeneca alleged that in the study used to substantiate comparative efficacy for Invokana 300mg vs sitagliptin (Schernthaner *et al*), sitagliptin was given as recommended in Section 4.2 of its SPC, while Invokana was not. This comparison created

a misleading impression, in breach of Clause 7.3, as it was not possible to draw conclusions on the comparative efficacy of these agents where Invokana was used in line with the licensed posology.

AstraZeneca noted that it had originally also alleged a breach of Clause 7.4 on this point given that, by Janssen's admission during inter-company dialogue, no data existed to substantiate these claims where Invokana was given in line with the licensed posology. AstraZeneca submitted that as the Panel ruled a breach of Clause 7.4 on a separate point from that alleged, it was unable to pursue this matter.

AstraZeneca alleged that the efficacy claims at issue for Invokana 300mg were presented prominently and constituted a core component of Janssen's promotional campaign. Given the totality of the above, it amounted to a failure to maintain high standards in breach of Clause 9.1.

AstraZeneca alleged that if the studies cited were used to support claims for the 300mg dose, it should be made clear that these results were obtained when the medicine was initiated in a manner different to that described in Section 4.2 of the SPC. Such data should be presented alongside data for Invokana 100mg.

RESPONSE FROM JANSSEN

Janssen submitted that AstraZeneca originally alleged that promotional claims for Invokana 300mg that were based upon the studies were misleading and in breach the Code. Given that the studies administered Invokana in a manner inconsistent with the SPC, AstraZeneca alleged that use of these studies to substantiate claims for the 300mg dose was misleading.

Janssen addressed the complaint on the grounds that it was acceptable to make efficacy claims based on the pivotal study results of a regulatory approved medicine when the study designs were not identical to the posology but still consistent with the SPC. Inter-company dialogue and the response to the Panel were based on AstraZeneca's original complaint that Janssen could not use pivotal registration trials to substantiate efficacy claims for Invokana 300mg, as patients had not been initiated on 100mg and then increased to 300mg, as per the posology of the Invokana SPC. Janssen submitted this was a direct challenge to a regulatory decision and tantamount to stating that Janssen could not promote Invokana 300mg. Furthermore, Janssen highlighted that such an approach would set a precedent that would affect the promotion of multiple regulatory approved medicines across the industry.

In its appeal, AstraZeneca had modified the complaint and introduced an altered position ie that pivotal studies using Invokana 300mg could be used to substantiate 300mg efficacy claims if a qualifying statement was added, which was secondary to the statement in Section 4.2 of SPC and was presented alongside data for 100mg.

Janssen was deeply concerned that AstraZeneca had broadened the grounds of its complaint and introduced past cases during the appeal process. Janssen did not have the opportunity to discuss these cases nor the AstraZeneca altered view during inter-company dialogue or at the initial PMCPA complaint.

Janssen noted that in the previous cases cited by AstraZeneca, the respondents were found in breach of the Code by promoting off-licence due to misleading presentation of 15-month efficacy data, which was outside the licensed treatment period of 12 months and did not fairly reflect the safety data. Janssen submitted that these cases were not comparable to this case.

Although Janssen accepted the rulings of breaches of Clauses 3.2 and 7.2 with regard to the claim 'Invokana 100mg and 300mg efficacy and flexibility at a single price', and accepted the Panel ruling that 'the claim 'flexibility' could be read as relating to the starting dose', it never claimed that patients could be initiated on 300mg. All materials included a statement confirming:

> 'The recommended starting dose of Invokana is 100mg once-daily. In patients tolerating Invokana 100mg once-daily, who have an eGFR ≥60/mL/min/1.73m^2 and need tighter glycaemic control, the dose can be increased to 300mg once-daily.'

Janssen corrected the statement from AstraZeneca that Janssen had admitted during inter-company dialogue, that no data existed to substantiate the claims where Invokana was given in line with the licensed posology. Janssen submitted that this did not accurately reflect the inter-company dialogue on 16 March 2016 as stated in the complaint above that there was '**no published**' evidence to suggest that there either was or was not a clinical meaningful difference in the observed efficacy of Invokana 300mg whether it was initiated at start or following dose regimen stated in the SPC (emphasis added).

Janssen submitted that it had unpublished data from a 26-week simulation study to assess the pharmacokinetic and pharmacodynamic HbA1c profiles of Invokana, using FDA approved modelling strategy. It demonstrated '… there are no differences in HbA1c reduction at 26 weeks between the groups started on 100mg and increased to 300mg and the group initiated and maintained at 300mg dose'. Janssen had not presented this data during inter-company dialogue because originally AstraZeneca complained that Janssen could not use the pivotal registration studies to substantiate Invokana 300mg efficacy claims due to differences in clinical trial design and SPC posology. The simulation study was not relevant to address AstraZeneca's original position.

Due to the altered position of the AstraZeneca complaint during the appeal process, and the misrepresentation by AstraZeneca that no data existed to substantiate the claims where Invokana was given in line with the licensed posology, Janssen submitted that it was now necessary to include new information for consideration: modelling data mentioned above; the pharmacodynamics and pharmacokinetics data in the SPC and a published phase 4 study (Rodbard *et al*, 2016) which showed

that clinical efficacy using a dose escalation schedule from Invokana 100mg to 300mg was consistent with previous pivotal studies where patients started on Invokana 300mg. These data were fundamental to Janssen's response to AstraZeneca's new and broadened challenge.

Janssen submitted that all Invokana promotional materials included data on 100mg and 300mg and always included information that patients should be started on 100mg Invokana in line with the licensed posology. Invokana 300mg was always represented together with 100mg and in the context of the licensed indication.

Janssen submitted that the two four page leavepieces at issue contained information about the efficacy of Invokana 100mg and 300mg with prominent information on the back page about the posology.

Janssen submitted that the one page advertisement contained information about the efficacy of Invokana 100mg and 300mg and had a statement:

> 'The recommended starting dose of Invokana is 100mg once-daily. In patients tolerating Invokana 100mg once-daily, who have an eGFR ≥60ml/min/1.73m^2 and need tighter glycaemic control, the dose can be increased to 300mg once-daily.'

Janssen acknowledged the flexibility claim in the advertisement could be misread and accepted the Panel's ruling and submitted that all other materials and claims were clear, not misleading and in line with the SPC.

Janssen emphasised that all 300mg efficacy claims made in the materials in question were presented within context of the licensed indication of Invokana and referenced to respective published clinical reports. Janssen did not promote the initiation of treatment on Invokana 300mg.

Efficacy claims of Invokana 300mg from pivotal studies were consistent with the marketing authorization, referenced to published data from the studies in the extensive clinical development programme, contained within SPC and were in line with the Code.

There were 9 pivotal phase 3 studies in the Invokana clinical development programme; patients were started and continued on a dose of either Invokana 100mg or 300mg, compared to the control group which started on either placebo or active comparators, for example sitagliptin (Schernthaner *et al*). The purpose of these studies was to examine efficacy and tolerability of Invokana.

Comprehensive efficacy and safety data collected in these pivotal studies formed part of the regulatory submission and data from these studies were included in the SPC as part of the marketing authorizations for Invokana. The clinical study designs and the results in conjunction with the SPC were reviewed by CHMP and authorized by the European Commission. The assessment was detailed in Section 2.5.4 Conclusions on the clinical efficacy of the European Public Assessment Report (EPAR) and stated:

> 'In the clinical program, both the 100mg and 300mg dose were shown to be efficient.'

Posology was detailed in Janssen promotional material, including its leavepieces, to ensure dosing information was available. Janssen had never claimed the patients could be initiated on 300mg.

Janssen submitted that it was clear from the pharmacodynamic and pharmacokinetic data detailed in the SPC that the glucose lowering effects of Invokana were maximal after day one of treatment and sustained over the treatment period. In addition, plasma concentration (Cmax) and area under curve (AUC) of Invokana increased in a dose proportional manner and patients reached a steady Cmax and AUC within 4-5 days after dose escalation from 100mg to 300mg.

Section 5.1 Pharmacodynamic properties stated:

> 'Fasting plasma glucose. In four placebo-controlled studies, treatment with canagliflozin as monotherapy or add-on therapy with one or two oral glucose-lowering medicinal products resulted in mean changes from baseline relative to placebo in FPG of -1.2mmol/L to -1.9mmol/L for canagliflozin 100mg and -1 9mmol/L to -2.4mmol/L for canagliflozin 300mg, respectively. These reductions were sustained over the treatment period and near maximal after the first day of treatment.'

Section 5.2 Pharmacokinetic properties stated:

> 'Plasma Cmax and AUC of canagliflozin increased in a dose-proportional manner from 50mg to 300mg. The apparent terminal half-life (t1/2) (expressed as mean ± standard deviation) was 10.6 ± 2.13 hours and 13.1 ± 3.28 hours for the 100mg and 300mg doses, respectively. Steady-state was reached after 4 days to 5 days of once-daily dosing with canagliflozin 100mg to 300mg.'

Janssen submitted that since the glucose lowering effect of Invokana was maximal after day one and a steady state plasma concentration was reached within 4-5 days following dose escalation, there was no scientific reason to expect a difference in clinical efficacy after 26 and 52 weeks if patients were started on 300mg vs if they were started at 100mg and the dose increased to 300mg.

Janssen reiterated that all efficacy claims in its promotional materials were made at endpoints (26 or 52 weeks), within the licensed indication of Invokana, referenced to respective published clinical reports.

Janssen submitted that as indicated above, there was no published data when inter-company dialogue took place to suggest a clinical meaningful difference when patients were initiated on Invokana 300mg or 100mg and increased to 300mg. However Janssen had unpublished modelling data which had established there were no expected differences

in HbA1c reduction at week 26 between initiating Invokana 300mg vs initiating Invokana 100mg and increasing to 300mg.

Janssen submitted that based on the pharmacokinetics, pharmacodynamics, the modelling data and now the published phase 4 study, it was possible to state what results would be expected if Invokana was used in line with SPC posology. Janssen never stated that efficacy claims were based on dosing similar to the posology in the SPC. Janssen thus did not agree that it was necessary to indicate that results from the pivotal studies were initiated in a manner different to Section 4.2 of the SPC. Janssen refuted breaches of Clauses 7.2, 7.3 and 9.1.

Janssen submitted that the inter-company dialogue was based on AstraZeneca's original complaint that the pivotal clinical trials could not be used to substantiate the efficacy claims of Invokana 300mg, due to differences between dosing schedule during study phase and the subsequent SPC posology. This was tantamount to stating that Janssen could not promote Invokana 300mg and therefore a direct challenge to a regulatory decision.

Janssen was concerned that AstraZeneca had now broadened its complaint, introduced new data and misrepresented inter-company dialogue; the focus of its appeal had deviated from its original complaint.

Janssen submitted that it had demonstrated that the promotional claims using the regulatory approved pivotal studies of Invokana 100mg or 300mg highlighted efficacy outcomes reported in the clinical studies, clearly referenced to corresponding published articles. These pivotal studies were the fundamental elements captured in the SPC and therefore promotion with these studies was aligned with the SPC. Janssen had never claimed that patients could start Invokana at 300mg.

Janssen submitted that it had demonstrated that there was no scientific reason to expect a difference in clinical efficacy at study endpoint if patients were started on Invokana 300mg vs if they were started at 100mg and the dose increased to 300mg based on the pharmacodynamic and pharmacokinetic data captured in the SPC and further supported by unpublished modelling data and a recently published phase 4 study (Rodbard *et al*).

Janssen submitted that it took patient safety extremely seriously. The 100mg dose was recommended as a precautionary measure and as such 300mg should only be considered in patients who tolerated 100mg and required additional glycaemic control. This was included in all Janssen's promotional materials.

Janssen submitted that claims related to the efficacy of Invokana 300mg were capable of substantiation, not misleading and consistent with the SPC, maintaining high standards and Janssen had not brought the industry into disrepute. Janssen refuted the breaches of Clauses 7.2, 7.3, 7.4, 9.1 and 2 of the Code.

FINAL COMMENTS FROM ASTRAZENECA

AstraZeneca provided further clarity as to why the use of supporting references in regard to efficacy claims for Invokana 300mg was misleading by describing circumstances in which their use might have been appropriate. AstraZeneca submitted that it had not broadened the scope of the complaint but had provided further and better particulars for consideration within the terms of the original complaint.

AstraZeneca stated that its allegation was, and remained, that the materials at issue were misleading because they could lead the audience to believe that the efficacy claims for Invokana 300mg could be expected when the medicine was used in accordance with its licence and the SPC. It was not acceptable to confuse and mislead the audience in such a way.

The very point of an appeal was to introduce further and better particulars that allowed the Appeal Board to consider whether the Panel ruling was correct and in that regard the introduction of past case rulings into the discussion was appropriate. AstraZeneca was surprised that Janssen had suggested otherwise and concerned that such an approach could undermine the logical and regulatory consistency of the Authority.

AstraZeneca submitted that Cases AUTH/2506/5/12 and AUTH/2507/5/12 were relevant to these proceedings as they indicated that references that contained off-licence data to substantiate claims must not be used in a misleading way or to imply the medicine could be used outside of its licence. In the present case, the references in the materials implied that efficacy could be achieved by using Invokana as per the SPC ie with a starting dose of 100mg.

AstraZeneca noted that Janssen had not appealed the Panel's ruling of a breach of Clause 3.2, ie it had accepted the Panel's view that the flexibility claim could be read as relating to the starting dose. AstraZeneca therefore questioned why Janssen denied having promoted that Invokana 300mg as a starting dose.

AstraZeneca had not been previously made aware of any results comparing the efficacy of Invokana given at 300mg from the point of treatment initiation with Invokana given at 100mg and subsequently stepped up to 300mg, ie in line with posology described in the SPC. Therefore, AstraZeneca refuted Janssen's assertion that its wording betrayed an attempt to misrepresent inter-company dialogue.

AstraZeneca noted the following with regard to the unpublished modelling results newly presented by Janssen:

- The data was dated 8 April 2016, ie it was apparently not available when the promotional items at issue were certified (September 2015, October 2015 and January 2016): it was not referenced in these items
- These results were not previously made available to AstraZeneca or to the Panel

- The promotional items at issue included claims around HbA1c, body weight and blood pressure reductions: the modelling study was restricted to HbA1c reduction only and so was not relevant to the claims about body weight or blood pressure effects
- The promotional items included comparative claims against sitagliptin: the model did not include comparative effects vs sitagliptin
- The results were at 26 weeks from treatment initiation. The promotional items at issue referred to results at 52 weeks.

AstraZeneca alleged that these results could not be extrapolated to substantiate the claims in the materials at issue relating to clinical benefits.

With regard to the phase 4 study, Rodbard *et al*:

- These data were available when the manuscript was submitted for publication on 21 March 2016, ie during the course of inter-company dialogue, yet were not previously made available to AstraZeneca or to the Panel: they were not referenced in the promotional items at issue
- The study examined patients on background therapy with metformin and sitagliptin. The claims made in the promotional items at issue related to patients either on no background therapy or on background therapy other than sitagliptin. These were not the same patient groups and therefore this study could not be used to substantiate the claims made in the promotional material at issue
- The promotional items included comparative claims against sitagliptin: the study did not include a sitagliptin arm and therefore could not be used to substantiate such claims
- This study did not include a comparative arm in which 300mg Invokana was given as a starting dose. It was therefore not possible to compare the efficacy of the two dosing regimens at issue on the basis of these results
- The results were at 26 weeks from treatment initiation. The promotional items at issue referred to results at 52 weeks.

AstraZeneca alleged that additional data and analysis which were not available when the promotional items in question were certified had been introduced and that this had the potential to confuse discussions around what claims could have been made at that time. The only relevance of this new information was to highlight that, when the items were certified, there were no data to substantiate efficacy claims for Invokana 300mg where it was used in accordance with the posology described in its SPC, ie with a starting dose of 100mg.

AstraZeneca alleged that the promotional items at issue were in breach of Clauses 7.2, 7.3, and 9.1 (Point 1), Clauses 7.4 and 9.1 (Point 2) and Clause 2 (Point 3).

APPEAL BOARD RULING

The Appeal Board noted that in the original complaint AstraZeneca alleged that promotional claims regarding Invokana 300mg based upon the pivotal studies were misleading as the starting dose in those studies was 300mg whereas the SPC required initiation on 100mg which could be increased to 300mg. In its appeal AstraZeneca's position changed as it now appeared to be of the view that the pivotal studies could be used provided that it was made clear that the results were obtained with a starting dose of 300mg which was different to that required in the SPC and this should be presented alongside data for the 100mg dose.

The Appeal Board did not consider that the cases cited by AstraZeneca were relevant as these related to the promotional use of 15 month data for a product where the SPC stated that treatment up to 12 months was recommended.

The Appeal Board noted the pharmacodynamic and pharmacokinetic data (Sections 5.1 and 5.2 of the SPC) that fasting plasma glucose reductions were near maximal after the first day of treatment and that steady state was reached after 4-5 days of treatment.

The Appeal Board considered on the very narrow grounds of the complaint that it was not necessarily inconsistent with the SPC to use studies with a starting dose of Invokana 300mg to support claims in the leavepiece as alleged. Similarly, the use of these references to substantiate claims for 300mg Invokana was not necessarily misleading as alleged. The Appeal Board upheld the Panel's ruling of no breach of Clause 7.2. The appeal on this point was unsuccessful.

With regard to the comparison with sitagliptin the Appeal Board noted its and the Panel's rulings above and decided that they were also relevant here. The Appeal Board upheld the Panel's ruling of no breach of Clause 7.3. The appeal on this point was unsuccessful.

In the circumstances, the Appeal Board did not consider that there had been a failure to maintain high standards. The Appeal Board upheld the Panel's ruling of no breach of Clause 9.1. The appeal on this point was unsuccessful.

2 Use of the word 'flexibility'

The September 2015 journal advertisement was headed 'Invokana 100mg and 300mg efficacy and flexibility* at a single price'. A footnote in very small print at the bottom of the page stated '*The recommended starting dose of Invokana is 100mg once daily. In patients tolerating Invokana 100mg once daily, who have a eGFR ≥60mL/min/1.73m^2 and need tighter glycaemic control, the dose can be increased to 300mg'.

The heading was followed by hanging signs representing cost (a £ sign in a circle) and reductions in HbA1c, kg and mmHg. There were then sections headed 'Invokana 100mg' and 'Invokana 300mg'. The Invokana 100mg section included favourable comparison in HbA1c, weight and blood pressure reductions vs sitagliptin in dual therapy as add-on therapy to metformin referenced to Lavalle-González *et al*. The Invokana 300mg section included favourable comparison with HbA1c, weight and blood pressure reductions with sitagliptin in dual and triple therapy, as add-on to metformin and as add-on to metformin and

sulphonylurea. Each section contained comparisons between the Invokana dose and sitagliptin.

The same claim appeared on the front page of the October 2015 leavepiece which was also followed by the hanging signs.

COMPLAINT

AstraZeneca alleged that 'flexibility' also breached various clauses of the Code. The advertisement used 'flexibility' in its title and the equal prominence given to the 100mg and 300mg doses implied that 300mg could be initiated and/or administered interchangeably with 100mg. AstraZeneca alleged this was inconsistent with the SPC. This impression was not negated by the footnote in substantially smaller font near the bottom of the page which stated:

> 'The recommended starting dose of invokana is 100mg once-daily. In patients tolerating Invokana 100mg once-daily, who have an eGFR ≥60ml/min/1.73m^2 and need tighter glycaemic control, the dose can be increased to 300mg once-daily.'

AstraZeneca stated that the same was true for the October 2015 leavepiece.

AstraZeneca stated that in inter-company dialogue (letter of 3 February 2016) Janssen asserted that the advertisement was not misleading and was in accordance with the terms of the Invokana marketing authorization but did not explain. Janssen acknowledged AstraZeneca's comment on the size of the footnote related to the claim on flexibility and agreed to consider this for future advertisements. AstraZeneca contended that this did not address the fundamental issue in relation to the advertisement.

AstraZeneca alleged that use of the word 'flexibility' constituted promotion outside the scope of the marketing authorization in breach of Clause 3.2. AstraZeneca alleged that the claim was misleading and in breach of Clause 7.2. Furthermore, as it was not possible to substantiate claims around 'flexibility': this constituted a breach of Clause 7.4. This demonstrated a failure to maintain high standards and a breach of Clause 9.1 was alleged.

RESPONSE

Janssen refuted the allegations that 'flexibility' when read in context, was misleading, inaccurate and unable to be substantiated. 'Flexibility' in the cited Invokana materials did not infer flexibility to start Invokana at either dosage in patients with type 2 diabetes.

The full claim was: 'Invokana 100mg and 300mg efficacy and flexibility* at a single price.' Janssen submitted that the use of word 'flexibility' in the context of this claim was within the requirements of the Code and not in breach of Clauses 3.2, 7.2, 7.4 and 9.1.

In August 2015, both the 100mg and 300mg Invokana became available at the same listed price, removing some NHS imposed barriers to prescribe Invokana 300mg in patients who required tighter glycaemic control.

In light of this background, the context of this claim was to show that both doses of Invokana were now available at the same price - in other words health professionals could prescribe Invokana 100mg dose for initiation and then, if appropriate, increase to 300mg for patients who would benefit from tighter diabetes control without the concern of additional cost. This allowed flexibility to tailor the dose according to patients' individual needs, in line with the posology, without worrying about cost increasing in line with the increasing dose. 'Flexibility' was footnoted to the posology to give health professionals clear guidance in the dosing instruction when higher dose should be used.

Janssen noted that the font size varied deliberately in the claim with 'flexibility' in smaller font because the key point was the cost. The structure of the sentence was quite clearly such that the Invokana 100mg dose was initiated first, as per the SPC.

Janssen did not agree that use of the word 'flexibility' implied that Invokana 300mg dose could be initiated and/or administered interchangeably with the 100mg dose. Posology of how Invokana was recommended to be used was clearly stated in all Invokana materials as well as in the advertisement and the October 2015 leavepiece cited by AstraZeneca. Furthermore, there was no market evidence or physician feedback to suggest that doctors had been misled. As such Janssen refuted the allegations of breaches of Clauses 3.2, 7.2, 7.4 and 9.1.

Invokana 300mg had been granted a marketing authorization. Janssen had not identified any examples of where promoting the 300mg dose in accordance with the licence represented a breach of high standards. Janssen maintained the use of word 'flexibility' in the context of the material could be substantiated.

Janssen submitted that it took patient safety extremely seriously, and would never 'deliberately misrepresent the facts' regarding safety issues, as alleged. There was no rationale as to why the company would want to do this, or why Invokana 300mg dose would be recommended as an initiation dose. The Invokana 100mg dose was recommended as a precautionary measure and as such 300mg should only be considered in those who tolerated 100mg and required additional glycaemic control. This was made clear in Janssen's promotional material.

PANEL RULING

The Panel considered that the claim in the advertisement ('Invokana 100mg and 300mg efficacy and flexibility at a single price)' did not make it sufficiently clear where each dose fitted in to the treatment pathway. It might be likely that when prescribing for new patients health professionals might start by using the 100mg dose as set out in the SPC. The Panel did not accept Janssen's submission that the claim was qualified by the use of the asterisk and its explanation regarding the recommended starting dose. It was a well-accepted principle under the Code that claims should not be qualified by

footnotes, they should be capable of standing alone as regards accuracy etc.

The Invokana SPC was clear that the recommended starting dose was 100mg once daily. There was no indication in the posology section as to how long the 100mg starting dose should be used before increasing it to 300mg in appropriate patients.

The Panel considered that the claim 'flexibility' could be read as relating to the starting dose and not, as submitted by Janssen, that some patients started on 100mg could increase their dose to 300mg and this would not mean an increase in cost. The Panel considered that the claim was misleading and inconsistent with the SPC. The Panel ruled breaches of Clauses 3.2 and 7.2 of the Code. As far as substantiation was concerned the Panel accepted that there was data relating to both doses and in relation to starting with the 300mg dose as referred to in Point 1 above. The Panel thus ruled no breach of Clause 7.4. This ruling was appealed.

On balance, the Panel did not consider that the claim meant that high standards had not been maintained and no breach of Clause 9.1 was ruled. This ruling was appealed.

APPEAL BY ASTRAZENECA

AstraZeneca noted that the Panel had agreed that 'flexibility' claims for Invokana 100mg and 300mg were misleading and inconsistent with the SPC, ie that the claim implied that Invokana could be started at a dose of either 100mg or 300mg, and ruled breaches of Clauses 3.2 and 7.2. AstraZeneca alleged that there were no data to support efficacy claims for the 300mg dose when it was given in accordance with the posology stated in the SPC, ie when a patient was initiated at a dose of 100mg and subsequently escalated to a dose of 300mg. Thus, the claim, which had already been ruled to be misleading could not be substantiated and was in breach of Clause 7.4.

AstraZeneca alleged that to imply that Invokana could be started at a dose higher than that recommended in the SPC amounted to a failure to maintain high standards, in breach of Clause 9.1.

AstraZeneca referred in particular to the EPAR for Invokana which noted that patients should be started on the 100mg dose for safety:

> 'Thus, some conditions existed in which a starting dose of 100mg should be used for safety reasons since drop in blood pressure and volume depletion or its sequelae could be more pronounced upon onset of treatment. Therefore a starting dose of 100mg was recommended for all patients as a precautionary measure and to simplify posology' (page 104).
>
> 'As a precautionary measure, a starting dose of 100mg is recommended for all patients' (pages 111-112).

AstraZeneca alleged that the importance of starting Invokana at 100mg dose for safety reasons must be made clear.

RESPONSE FROM JANSSEN

Janssen accepted the Panel ruling that the claim flexibility could be read as relating to the starting dose and therefore accepted breaches of Clauses 3.2 and 7.2 of the Code. However, the dosing information was included in the advertisement as in all promotional materials:

> 'The recommended starting dose of Invokana is 100mg once-daily. In patients tolerating Invokana 100mg once-daily, who have an eGFR ≥60ml/min/1.73m^2 and need tighter glycaemic control, the dose can be increased to 300mg once-daily.'

Janssen submitted that it did not make claims that patients could be initiated on 300mg and as demonstrated above, there was evidence to support no difference in the efficacy if Invokana was given in accordance with SPC posology. Hence, efficacy claims of Invokana 300mg was capable of substantiation and high standards had been maintained.

Therefore, Janssen refuted breaches of Clauses 7.4 and 9.1.

FINAL COMMENTS FROM ASTRAZENECA

See AstraZeneca's final comments at Point 1 above.

APPEAL BOARD RULING

The Appeal Board noted the Panel's rulings of breaches of Clauses 7.2 and 3.2 had been accepted by Janssen. AstraZeneca's appeal related to the lack of data to support efficacy claims for Invokana 300mg when initiated at 100mg and subsequently increased to a dose of 300mg. The Appeal Board agreed with the Panel and accepted that there was data relating to both doses and in relation to starting with the 300mg dose as referred to in Point 1 above. It considered that in the circumstances there was data to substantiate the efficacy claims. The Appeal Board thus upheld the Panel's ruling of no breach of Clause 7.4. The appeal on this point was unsuccessful.

Again the Appeal Board noted the Panel's rulings of breaches of Clauses 7.2 and 3.2 of the Code as well as its ruling of no breach of Clause 7.4.

The Appeal Board did not consider that, in the circumstances, high standards had not been maintained and it upheld the Panel's ruling of no breach of Clause 9.1. The appeal on this point was unsuccessful.

3 Seriousness of breaches

COMPLAINT

AstraZeneca alleged that use of these promotional claims represented a deliberate attempt to misrepresent the facts. Furthermore, AstraZeneca noted that the EPAR for Invokana twice stated that patients should always be initiated on the 100mg dose for safety reasons.

'Thus, some conditions exist in which a starting dose of 100mg should be used for safety reasons since drop in blood pressure and volume depletion or its sequelae could be more pronounced upon onset of treatment. Therefore a starting dose of 100mg is recommended for all patients as a precautionary measure and to simplify posology.' (Page 104)

'As a precautionary measure, a starting dose of 100mg is recommended for all patients.' (Page 111)

AstraZeneca therefore alleged that use of the word 'flexibility' (Point 2) in this way had the potential to compromise patient safety. AstraZeneca alleged that Janssen's actions had the potential to bring discredit to, and reduce confidence in, the pharmaceutical industry in breach of Clause 2.

RESPONSE

Janssen submitted that the allegations raised by AstraZeneca were unfounded. Janssen promotional materials and claims were in alignment with the Code. As such, Janssen refuted the allegation of breach of Clause 2.

PANEL RULING

The Panel noted its rulings in Points 1 and 2 above. It did not consider that the use of the word 'flexibility' compromised patient safety such that Janssen had brought discredit upon or reduced confidence in the pharmaceutical industry. The Panel therefore ruled no breach of Clause 2 of the Code. This ruling was appealed.

APPEAL BY ASTRAZENECA

AstraZeneca appealed the Panel's ruling of no breach of Clause 2 in relation to all misleading claims that implied that Invokana could be initiated at a dose of 300mg and the cumulative breaches in this case. Clause 2 was reserved as a sign of particular censure and AstraZeneca alleged that claims that might impact the safety of patients fell in to this category.

RESPONSE FROM JANSSEN

Janssen reiterated that all promotional materials for Invokana included data on Invokana 100mg and 300mg. Janssen took patient safety extremely seriously and the materials always included information that patients should be initiated on 100mg Invokana in line with the approved posology. Janssen had not claimed that patients could be initiated on 300mg and as demonstrated above, there was evidence to support no difference in the efficacy if Invokana was given in accordance with SPC posology.

Hence, Janssen submitted that patient safety and high standards had been maintained so there had been no breach of Clause 2

FINAL COMMENTS FROM ASTRAZENECA

See AstraZeneca's final comments at Point 1 above.

APPEAL BOARD RULING

The Appeal Board noted its and the Panel's rulings in Points 1 and 2 above. It did not consider that the use of the word 'flexibility' compromised patient safety such that Janssen had brought discredit upon or reduced confidence in the pharmaceutical industry. The Appeal Board therefore upheld the Panel's ruling of no breach of Clause 2 of the Code. The appeal on this point was unsuccessful.

Complaint received **11 April 2016**

Case completed **21 July 2016**