CASE AUTH/2569/12/12

MERCK SHARP & DOHME v NOVO NORDISK

Promotion of Victoza

Merck Sharp & Dohme complained about a Victoza (liraglutide) detail aid produced by Novo Nordisk.

The detail aid was headed 'The value of Victoza' and referred to the comparative effectiveness of oral antidiabetic medicines and glucagon-like peptide-1 (GLP-1) receptor agonists after metformin failure. Page 2 was headed 'Uncontrolled diabetes and its complications are a major health and economic burden'. Reference was made to the effects of a 1% reduction in HbA_{1c}, a 5% reduction in weight and reduced hypos (hypoglycaemic episodes). Page 3 referred to the failure of patients to reach their goals. This was followed by 'Victoza 1.2mg delivers benefits for patients with type 2 diabetes' followed by the claim 'With Victoza 1.2mg in combination with metformin, 32% of patients achieved the target of HbA_{1c} <7%, weight loss or neutrality, and no hypoglycaemia' referenced to Zinman *et al* (2011). The page ended with three separate bullet points 'Reach their HbA_{1c} target of <7%', 'Experience weight loss or no weight gain' and 'Experience no increase in the risk of hypoglycaemia'. Beneath these bullet points were three red boxes each linked with a plus sign which stated 'HbA_{1c}<7%' 'weight loss or neutrality' and 'no hypos' respectively. Beneath the boxes was the statement 'Triple composite endpoint used in Zinman *et al*, 2011'. The red boxes appeared just above the Victoza brand logo which was the same shade of red.

Page 4 was headed 'More patients reach treatment targets with Victoza vs other treatments'. It compared a number of classes of oral antidiabetic medicines vs Victoza in relation to reaching the composite endpoint defined in Zinman *et al* which was described as 'Comparative effectiveness: Percentage of patients achieving HbA1c,< 7%, with no weight gain and no hypoglycaemic episodes'. The Victoza figure was 32%. The results for the other medicines shown were between 6% and 25%. The figure for DPP-IV inhibitor (Merck Sharp & Dohme's product sitagliptin (Januvia), 100mg daily) was 11%. The comparison was referenced to Zinman *et al*.

Page 5 was headed with the three coloured boxes showing the triple composite endpoint used on page 3. This was followed by the heading 'Fewer patients need to be treated with Victoza 1.2mg to get one patient to targets of HbA_{1c} <7%, weight loss or neutrality, and no hypoglycaemia compared with other treatments'. The figures in the chart that followed was 3 people for Victoza; the figures for the other products were between 4 and 17. The claim was referenced to data on file (2011).

Page 6 was headed with the three coloured boxes showing the triple composite endpoint used on pages 3 and 5. This was followed by the heading 'Victoza 1.2mg is a cost-effective treatment for type 2 diabetes'.

Page 8 (the back cover) was headed 'Delivering more value than you might think' followed by 'Victoza helps patients with type 2 diabetes reach their treatment targets' and 'More patients reach HbA_{1c} targets of <7% with weight loss or neutrality with Victoza 1.2mg than with all comparators, without increasing the rate of hypoglycaemia'. A number of claims followed finishing in a white box with '£To give patients an efficacious and cost-effective type 2 diabetes treatment post-metformin failure, consider starting them on Victoza today'. This was immediately followed by the red coloured boxes showing the triple composite endpoint used on pages 3, 5 and 6.

The detailed response from Novo Nordisk is given below.

Merck Sharp & Dohme was concerned about the substance and presentation of a post-hoc meta-analysis (Zinman *et al*), in which seven liraglutide trials were re-evaluated using a composite endpoint (achievement of HbA_{1c} goal (defined as 7%), absence of hypoglycaemia and absence of weight gain) in an attempt to derive cost-effectiveness data for liraglutide vs the various comparators used in the studies.

Merck Sharp & Dohme was concerned that of the seven trials included in the analysis, (the LEAD (liraglutide effect and action in diabetes) -3 Mono trial, which contributed approximately 11% of the total analysis population) was a study of liraglutide monotherapy. As liraglutide was not licensed for monotherapy in the UK, inclusion of data was not in accordance with the Victoza marketing authorization. Furthermore, the use of such data could have biased the findings in favour of liraglutide as the efficacy of antidiabetic agents would be expected to be greater with earlier therapy; the reported incidence of hypoglycaemia increased with increasing duration of diabetes. None of the comparator agents in the analysis were evaluated as monotherapy.

The Panel noted that Zinman *et al* was a prespecified meta-analysis of 26 week patient level data from seven trials evaluating Victoza with commonly used treatments for type 2 diabetes adjusting for baseline HbA_{1c} and weight, for a composite outcome of HbA_{1c}<7%, no weight gain and no hypoglycaemic events. The authors noted that although the differences in patient populations between the trials, in terms of previous antidiabetic therapy, were included as fixed effects in their analysis, there were limits to the conclusions that could be drawn from studies that differed in terms of background therapy.

The results showed that at 26 weeks, 40% of patients taking liraglutide 1.8mg and 32% of those taking 1.2mg achieved the composite outcome vs 6-25% of the comparators. As none of the studies used

metformin as an active comparator Zinman *et al* was unable to objectively evaluate liraglutide vs metformin. The composite endpoint was chosen as it related to clinical issues of concern for both patient and physician. The authors stated that long-term outcome studies were required to determine if the improvement in the composite outcome reported would have significant long-term effects on clinical outcomes.

The Panel noted the patient numbers and that LEAD-3 Mono contributed more patients to the liraglutide 1.2mg group than any of the other studies. Liraglutide was not indicated as monotherapy. The Panel noted Merck Sharp & Dohme's comments about whether the monotherapy patient data was sufficiently similar to the combination data. Novo Nordisk provided data to show that LEAD-3 Mono did not appear to be an outlier with regard to decrease in HbA_{1c} and that in the studies included in Zinman *et al* minor hypoglycaemia incidence did not consistently increase with increasing duration of diabetes.

The Panel noted that the detail aid did not refer to the use of Victoza as monotherapy. The licensed indication for Victoza as combination therapy was stated on the front page.

The Panel did not consider that reporting the results of Zinman *et al per se* promoted Victoza for an unlicensed indication or that the promotional material was inconsistent with the summary of product characteristics (SPC). Thus on the narrow grounds of the allegation it ruled no breach of the Code.

Merck Sharp & Dohme was concerned that the composite endpoint used in Zinman *et al* had been reproduced in prominent red boxes on several pages of the detail aid. This associated the substance of the composite endpoint with liraglutide itself, effectively representing a claim. One of the components of the endpoint was 'No hypoglycaemia', whereas hypoglycaemia was cited as a 'common' or 'very common' adverse effect in the Victoza SPC, Merck Sharp & Dohme thus alleged that this presentation was misleading.

The Panel examined the presentation of the composite endpoint in the detail aid. Each component was highlighted in a red box and the three boxes were joined with two plus signs. The same shade of red was used for some claims for Victoza and for the product logo. The Panel considered that the content, colouring and/or positioning of the red boxes would lead readers to conclude that all Victoza patients would have HbA_{1c} <7%, lose weight or be weight neutral and have no hypos.

The Panel noted that the Victoza SPC stated that Victoza in combination with metformin, metformin and glimepiride or metformin and rosiglitazone was associated with sustained weight reduction over the duration of studies (range 1-2.8kg). The SPC also stated that Victoza 1.2mg and glimepiride increased mean body weight by 0.32kg. The SPC listed hypoglycaemia as a common adverse reaction with Victoza and glimepiride and Victoza with metformin and rosiglitazone. It was listed as very common with Victoza with metformin and glimepiride.

The Panel considered that the presentation of the composite endpoint throughout the detail aid was, in effect, a claim for Victoza and misleading as alleged. The Panel did not consider that the footnote to the red boxes, 'Triple composite endpoint used in Zinman *et al*, 2011', negated the impression. A breach of the Code was ruled.

Merck Sharp & Dohme was also concerned about the comparison with Januvia. It believed that the use of a composite endpoint added nothing to the findings of the original study (Pratley *et al* 2010), given that there were no differences in the incidences of weight gain and hypoglycaemia between the liraglutide and sitagliptin study arms. Merck Sharp & Dohme alleged that the presentation of the liraglutide vs sitagliptin comparison was misleading, and possibly disparaging.

The Panel noted that pages 4 and 5 compared Victoza with a number of treatments, including Merck Sharp & Dohme's product sitagliptin. Pratley *et al* stated that mean weight loss after 26 weeks was significantly greater with Victoza than sitagliptin ($p < 0.0001$ for both doses of Victoza). The Panel noted the additional Novo Nordisk data on file whereby 20.8% of patients on Victoza 1.2mg plus metformin, 16.1% of patients on Victoza 1.8mg plus metformin and 37.4% of patients on sitagliptin plus metformin had increased body weight. The figures for decrease in body weight or no change were 79.2%, 84% and 62.6% respectively.

The Panel considered that there appeared to be a difference between the parties with regard to the weight data. The use of composite endpoints was not prohibited under the Code. Zinman *et al* showed the composite endpoint differences between Victoza 1.2mg and sitagliptin. It did not appear that this difference was only due to differences between the products in relation to attainment of HbA_{1c}<7% as alleged by Merck Sharp & Dohme. Whilst noting its rulings above, the Panel did not consider that the comparison with sitagliptin was misleading as alleged. Nor did the comparison disparage sitagliptin. No breaches of the Code were ruled.

Merck Sharp & Dohme Limited complained about a Victoza (liraglutide) detail aid (ref UK/LR/0212/0048) produced by Novo Nordisk Limited. Novo Nordisk confirmed in inter-company dialogue that whilst the detail aid had been withdrawn from circulation, similar items remained in use. The complaint was thus referred to the Panel.

Victoza (for injection) was indicated for the treatment of adults with type 2 diabetes to achieve glycaemic control: in combination with metformin or a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin or sulphonylurea; in combination with metformin and a sulphonylurea or metformin and a thiazolidinedione in patients with insufficient glycaemic control despite dual therapy.

The detail aid was headed 'The value of Victoza' and referred to the comparative effectiveness of oral antidiabetic medicines and glucagon-like peptide-1 (GLP-1) receptor agonists after metformin failure. Page 2 was headed 'Uncontrolled diabetes and its complications are a major health and economic burden'. It included a statement that effective treatment was associated with reduced complications and side effects. Reference was made to the effects of a 1% reduction in HbA_{1c} a 5% reduction in weight and reduced hypos (hypoglycaemic episodes). Page 3 referred to the failure of patients to reach their goals. This was followed by 'Victoza 1.2mg delivers benefits for patients with type 2 diabetes' followed by the claim 'With Victoza 1.2mg in combination with metformin, 32% of patients achieved the target of HbA_{1c} <7%, weight loss or neutrality, and no hypoglycaemia' referenced to Zinman *et al* (2011). The page ended with three separate bullet points 'Reach their HbA_{1c} target of <7%', 'Experience weight loss or no weight gain' and 'Experience no increase in the risk of hypoglycaemia'. Beneath these bullet points were three red boxes each linked with a plus sign which stated 'HbA_{1c}<7%' 'weight loss or neutrality' 'no hypos' respectively. Beneath the boxes was the statement 'Triple composite endpoint used in Zinman *et al*, 2011'. The red boxes appeared just above the Victoza brand logo which was the same shade of red.

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Page 5 was headed with the three coloured boxes showing the triple composite endpoint used on page 3. This was followed by the heading 'Fewer patients need to be treated with Victoza 1.2mg to get one patient to targets of HbA_{1c} <7%, weight loss or neutrality, and no hypoglycaemia compared with other treatments'. The figures in the chart that followed was 3 people for Victoza; the figures for the other products were between 4 and 17. The claim was referenced to data on file (2011).

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1 Use of monotherapy data

COMPLAINT

Merck Sharp & Dohme stated that its concerns, and the reasons underlying them, were set out in inter-company dialogue and summarized below.

Merck Sharp & Dohme was concerned about the substance and presentation of a post-hoc meta-analysis (Zinman *et al*), in which seven liraglutide trials were re-evaluated using a composite endpoint (achievement of HbA_{1c} goal (defined as 7%), no hypoglycaemia and no weight gain) in an attempt to derive cost-effectiveness data for liraglutide vs the various comparators used in the studies.

Merck Sharp & Dohme was concerned that of the seven trials included in the analysis, one (the LEAD (liraglutide effect and action in diabetes) -3 Mono trial, which contributed approximately 11% of the total analysis population) was a study of liraglutide monotherapy vs glimepiride. Merck Sharp & Dohme alleged that as liraglutide was not licensed for monotherapy in the UK, inclusion of data from this trial was not in accordance with the marketing authorization for liraglutide in breach of Clause 3.2. Novo Nordisk had stated that the LEAD-3 data were included in an effort to be comprehensive and that monotherapy use was not specifically promoted in the detail aid. Nevertheless, Merck Sharp & Dohme did not believe that such considerations could exempt a company from its obligation under the Code not to use off-label data in its promotional materials.

Furthermore, the use of such data could have biased the findings in favour of liraglutide because the efficacy of any antidiabetic agent would be expected to be greater with earlier therapy; it was well accepted that the reported incidence of hypoglycaemia increased with increasing duration of diabetes. Both of these factors would have affected the comparative liraglutide results measured against the composite endpoint, particularly as (apart from glimepiride) none of the other comparator agents in the analysis were evaluated as monotherapy.

Merck Sharp & Dohme had suggested to Novo Nordisk that the Zinman *et al* analysis be re-calculated without the LEAD-3 data, but it had declined to do so.

RESPONSE

Novo Nordisk noted that the detail aid did not promote the use of liraglutide as a monotherapy treatment option for type 2 diabetes. The licensed indication for liraglutide was clearly stated on the front page.

Zinman *et al*, was a meta-analysis of all the available liraglutide phase 3 trials, including LEAD-3 Mono. The National Institute for Health and Clinical Excellence (NICE) Methods Guide for Technology Appraisal defined meta-analysis as a statistical technique for combining (pooling) the results of a number of studies that addressed the same question and reported on the same outcomes to produce a more precise summary estimate of the effect on a particular outcome.

The Zinman *et al* data was used in the detail aid to show a comparison of liraglutide 1.2mg in reaching the clinically important outcome of achieving a target HbA_{1c} without weight gain or hypoglycaemia vs other available treatment options including glimepiride, rosiglitazone, sitagliptin, exenatide and glargine. When the meta-analysis was conducted there were seven phase 3 trials available which included 4,625 patients. Without the meta-analysis, liraglutide could not be collectively compared to all the aforementioned treatments; instead it could only be compared to individual medicines. Novo Nordisk noted that LEAD-3 Mono contributed just 10.7% (498) of the overall number of patients in the analysis.

In relation to hypoglycaemia, Novo Nordisk provided a table summarising the data from the studies used in Zinman *et al* which had been generated by referring to the individual published studies but also data on file from the Integrated Clinical Trial Report. With an increase in the duration of diabetes there was no consistent decrease in liraglutide efficacy (measured as HbA_{1c} decrease or as the percentage of patients reaching <7% HbA_{1c}, as in Zinman *et al*) or increase in reported hypoglycaemia when LEAD-3 was compared with the other studies. When referring to the summary of liraglutide trial data, Novo Nordisk noted that the data on efficacy for LEAD-3 did not appear to be an outlier. Furthermore, the rates of hypoglycaemia were higher in LEAD-3 compared with most of the other studies, with the exception of LEAD-5 and LEAD-6 where liraglutide was used concomitantly with a sulphonylurea.

Taking the above into account, it was likely that by excluding LEAD-3 data, the outcome of Zinman *et al* would have favoured liraglutide even more. Novo Nordisk reiterated that by including all relevant studies in Zinman *et al*, it wanted to be as comprehensive as possible and not be accused of selectively using the data.

Meta-analysis was commonly used in NICE technology appraisals. The Methods Guide for Technology Appraisal outlined the following: 'Synthesis of outcome data through meta-analysis is appropriate provided there are sufficient relevant and valid data that use measures of outcome that are comparable'.

As more new diabetes treatments became available there would be an increasing demand to compare these with the efficacy of existing therapies. It would never be possible to perform comparative trials against all existing therapies and therefore these analyses would increasingly rely on network meta-analyses to guide payers and health professionals.

Network meta-analysis built on the principles of meta-analysis and created an analysis that compared two or more interventions using a combination of direct evidence (from head-to-head trials of the interventions of interest) and indirect evidence (trials that did not compare the interventions of interest directly in head-to-head trials).

The NICE Methods Guide stated that the principles of good practice for standard meta-analyses should also be followed in mixed and indirect treatment comparisons. Furthermore, ISPOR (International Society for Pharmacoeconomics and Outcomes Research) Taskforce recommendations on conducting indirect-treatment-comparison and network meta-analysis studies stated that unlicensed treatments in some instances might contribute to the evidence network.

Network meta-analysis in diabetes was complex due to the number of available treatment options and the complexity of the treatment pathway. If such analysis could only include evidence for licensed indications, this would add greater complexity to what would already be a complex meta-analyses if the statisticians had to assess whether all of the identified studies complied fully with the licensed indication. This would pose even greater problems where studies might report the results of trials where the licensed vs unlicensed population was combined and patient level data was not available. Furthermore, if it was ruled that meta-analysis and network meta-analysis used for promotional purposes should only be based on evidence from licensed indications, this might create different efficacy and safety values to those in peer reviewed publications and/or health technology submissions. This could create confusion and question the credibility of such analyses thereby creating a controversial issue not only for Novo Nordisk but for all of the companies going forward.

Based on the above, Novo Nordisk did not believe that it had promoted liraglutide outside of the marketing authorization and denied a breach of Clause 3.2.

PANEL RULING

The Panel noted that Zinman *et al* was a prespecified meta-analysis of 26 week patient level data from seven trials evaluating Victoza with commonly used treatments for type 2 diabetes adjusting for baseline HbA_{1c} and weight, for a composite outcome of HbA_{1c}<7%, no weight gain and no hypoglycaemic events. The authors noted that although the differences in patient populations between the trials, in terms of previous exposure to antidiabetic therapy, were included as fixed effects in their analysis, there were limitations to the conclusions that could be drawn from studies that differed in terms of background therapy.

The results showed that at 26 weeks, 40% of patients taking liraglutide 1.8mg and 32% of those taking 1.2mg achieved the composite outcome vs 6-25% of the comparators. As none of the studies used metformin as an active comparator Zinman *et al* was

unable to objectively evaluate the performance of liraglutide vs metformin with this composite outcome approach. The authors chose the composite endpoint as it specifically related to clinical issues of concern for both patient and physician. The authors stated that long-term outcome studies were required to determine if the improvement in the composite outcome reported would have significant long-term effects on clinical outcomes.

The Panel noted that the detail aid promoted Victoza 1.2mg. Zinman *et al* evaluated the results of 4,625 patients of which 1,581 were on Victoza 1.8mg and 1,117 were on Victoza 1.2mg. LEAD-3 Mono studied 251 patients taking Victoza 1.2mg and 247 patients taking Victoza 1.8mg. Thus LEAD-3 Mono was carried out on 251/1,117 ie 22.5% of Victoza 1.2mg patients. LEAD-3 Mono contributed more patients to the liraglutide 1.2mg group than any of the other studies. Liraglutide was not indicated as monotherapy. The Panel noted Merck Sharp & Dohme's comments about whether the monotherapy patient data was sufficiently similar to the combination data given that monotherapy was used earlier in the treatment pathway and the efficacy of any antidiabetic therapy would be expected to be greater with earlier therapy and that the reported incidence of hypoglycaemia increased with increasing duration of diabetes. Novo Nordisk provided data to show that LEAD-3 Mono did not appear to be an outlier with regard to decrease in HbA_{1c} and that in the studies included in Zinman *et al* minor hypoglycaemia incidence did not consistently increase with increasing duration of diabetes.

The Panel noted that the detail aid did not refer to the use of Victoza as monotherapy. The licensed indication for Victoza as combination therapy was stated on the front page.

The Panel noted that Zinman *et al* was incorrectly referenced in the list of references as Zinman *et al* (2012). Zinman *et al* included a study (LEAD-3, Mono), that investigated Victoza as monotherapy. The Panel did not consider, however, that reporting the results of Zinman *et al per se* promoted Victoza for an unlicensed indication or that the promotional material was inconsistent with the summary of product characteristics (SPC). Thus on the narrow grounds of the allegation it ruled no breach of Clause 3.2.

2 Composite endpoint claims

COMPLAINT

Merck Sharp & Dohme was concerned that the composite endpoint used in Zinman *et al* had been reproduced in prominent red boxes on several pages of the detail aid. There was no reason for this highly unusual practice other than to associate, in the reader's mind, the substance of the composite endpoint with liraglutide itself, effectively representing a claim. Given that one of the components of the composite endpoint was 'No hypoglycaemia', whereas hypoglycaemia was cited as a 'common' or 'very common' adverse effect in the Victoza SPC, Merck Sharp & Dohme alleged that this presentation was potentially highly misleading in breach of Clause 7.2. Merck Sharpe & Dohme did not consider that Novo Nordisk's offer to embolden the clarifying statement that appeared under each occurrence, would significantly mitigate the clear overall impression given by the manner in which the composite endpoint was used in the detail aid.

COMPLAINT

Merck Sharp & Dohme was concerned that the composite endpoint used in Zinman *et al* had been reproduced in prominent red boxes on several pages of the detail aid. There was no reason for this highly unusual practice other than to associate, in the reader's mind, the substance of the composite endpoint with liraglutide itself, effectively representing a claim. Given that one of the components of the composite endpoint was 'No hypoglycaemia', whereas hypoglycaemia was cited as a 'common' or 'very common' adverse effect in the Victoza SPC, Merck Sharp & Dohme alleged that this presentation was potentially highly misleading in breach of Clause 7.2. Merck Sharpe & Dohme did not consider that Novo Nordisk's offer to embolden the clarifying statement that appeared under each occurrence, would significantly mitigate the clear overall impression given by the manner in which the composite endpoint was used in the detail aid.

RESPONSE

Novo Nordisk stated that the composite endpoint within the red box was displayed at relevant points in the detail aid to remind the user of the composite endpoint of Zinman *et al*. Merck Sharp & Dohme claimed that this misled the reader into associating the endpoints with liraglutide itself. Feedback from health professionals had highlighted that the notion of a composite endpoint was not easily understood, so this provided an apt reminder of the three outcomes combined in the endpoint. The red box was only used at the points where the composite endpoint data was shown and was clearly referenced to Zinman *et al*. Novo Nordisk disagreed that detailing the composite endpoint in this way was in breach of Clause 7.2.

PANEL RULING

The Panel examined the presentation of the composite endpoint in the detail aid. Each component of the endpoint was highlighted in a red box and the three boxes were joined with two plus signs. The same shade of red was used for some claims for Victoza and for the product logo. The Panel considered that the content, colouring and/or positioning of the red boxes would lead readers to conclude that all Victoza patients would have HbA_{1c} <7%, lose weight or be weight neutral and have no hypos. In this regard the Panel noted that on page 3 in particular, the red boxes describing the composite endpoint 'HbA_{1c}<7% + weight loss or neutrality + no hypos' appeared immediately after the claim 'Victoza 1.2mg delivers benefits for patients with type 2 diabetes' and just above the product logo. Given the positioning and use of colour, the reader would link all three together. The back page of the detail aid was

headed, in red, 'Delivering more value than you might think'. The three red boxes appeared on the lower half of the page and the red product logo was in the bottom right hand corner. Again the Panel considered that the reader's eye would be drawn to all three and 'HbA_{1c} <7% + weight loss or neutrality + no hypos' would be seen as a claim for Victoza ie delivering more than the reader might think. Whilst Zinman *et al* had shown that some patients on Victoza 1.2mg would achieve the composite endpoint, it was only in a minority ie 32%.

The Panel noted that the Victoza SPC stated that Victoza in combination with metformin, metformin and glimepiride or metformin and rosiglitazone was associated with sustained weight reduction over the duration of studies (range 1-2.8kg). The SPC also stated that Victoza 1.2mg and glimepiride increased mean body weight by 0.32kg. The SPC listed hypoglycaemia as a common adverse reaction with Victoza and glimepiride and Victoza with metformin and rosiglitazone. It was listed as very common with Victoza with metformin and glimepiride.

The Panel considered that the presentation of the composite endpoint throughout the detail aid was, in effect, a claim for Victoza and misleading as alleged. The Panel did not consider that the footnote to the red boxes, 'Triple composite endpoint used in Zinman *et al*, 2011', negated the impression. A breach of Clause 7.2 was ruled.

3 Comparison with sitagliptin

COMPLAINT

Merck Sharp & Dohme was also concerned about the comparison with its product sitagliptin (Januvia). It believed that the use of a composite endpoint added nothing to the findings of the original study (Pratley *et al* 2010), given that there were no differences in the incidences of weight gain and hypoglycaemia between the liraglutide and sitagliptin study arms. Its position was set out in detail in inter-company dialogue. Novo Nordisk had declined to make it clear that there were no differences between the two medicines in these parameters. Merck Sharp & Dohme alleged that the presentation of the liraglutide vs sitagliptin comparison was misleading, and possibly disparaging, in breach of Clauses 7.2 and 8.1.

RESPONSE

Novo Nordisk submitted that in Pratley *et al*, liraglutide significantly decreased body weight compared with sitagliptin. In addition, data from the ICTR (Integrated Clinical Trial Report) for Pratley *et al* showed that 37.4% of patients gained weight in the sitagliptin arm compared with 20.8% and 16.1% in the liraglutide 1.2mg and 1.8mg arms respectively. This clearly demonstrated that liraglutide was superior compared with sitagliptin in two items of the composite endpoint (percentage of patients reaching target of HbA_{1c} <7% and number of patients without weight gain). As the results relating to weight gain had not been published previously, including this as part of Zinman *et al* added to the body of evidence to demonstrate the efficacy and safety of liraglutide vs other available treatments. Novo Nordisk did not consider that the presentation of the liraglutide vs sitagliptin data in the detail aid was either misleading or disparaging. Novo Nordisk therefore denied a breach of Clauses 7.2 and 8.1.

PANEL RULING

The Panel noted that pages 4 and 5 compared Victoza with a number of treatments, including Merck Sharp & Dohme's product sitagliptin. Pratley *et al* stated that mean weight loss after 26 weeks was significantly greater with Victoza than sitagliptin ($p < 0.0001$ for both doses of Victoza). The Panel noted the additional Novo Nordisk data on file whereby 20.8% of patients on Victoza 1.2mg plus metformin, 16.1% of patients on Victoza 1.8mg plus metformin and 37.4% of patients on sitagliptin plus metformin had increased body weight. The figures for decrease in body weight or no change were 79.2%, 84% and 62.6% respectively.

The Panel considered that there appeared to be a difference between the parties with regard to the weight data. The use of composite endpoints was not prohibited under the Code. Zinman *et al* showed the composite endpoint differences between Victoza 1.2mg and sitagliptin. It did not appear that this difference was only due to differences between the products in relation to attainment of HbA_{1c}<7% as alleged by Merck Sharp & Dohme. Whilst noting its ruling in Point 2 above, the Panel did not consider that the comparison with sitagliptin was misleading as alleged. No breach of Clause 7.2 was ruled. Nor did the comparison disparage sitagliptin and no breach of Clause 8.1 was ruled.

Complaint received **17 December 2012**

Case completed **25 February 2013**

ANONYMOUS HEALTH PROFESSIONAL v PHARMACOSMOS

Symposium invitation

An anonymous, non-contactable complainant who described themselves as a health professional complained about an invitation to a Pharmacosmos symposium at a European congress to take place in Vienna, February 2013. The invitation asked 'Can we optimize treatment with single high dose intravenous iron in IBD [inflammatory bowel disease] patients? – *New data from clinical trials'.* Pharmacosmos marketed Monofer (iron as iron (III) isomaltoside 100) and CosmoFer (iron dextran)). Both products were for the intravenous treatment of iron deficiency and both could be administered as total dose infusions.

The complainant stated that the material was supposed to be new and therefore he/she did not understand how it could be discussed or promoted until published and licensed.

The detailed response from Pharmacosmos is given below.

The Panel noted that the front page of the flyer featured a headline banner which read 'Invitation'. The reader was then invited to save the date for the Pharmacosmos symposium followed by the statement 'Can we optimize treatment with single high dose intravenous iron in IBD patients? - *New data from clinical trials.*' The background picture was of someone adjusting the flow of an intravenous drip. The reverse featured similar details about the date, time and location of the symposium above corporate information about Pharmacosmos and referred to treatment options with maximum efficacy, convenience and safety for patients and professionals. Readers were invited to visit the corporate website for more information.

Although the Panel noted that it was confined to considering the content of the flyer it further noted that discussion or promotion of medicines based on unpublished clinical data was not universally prohibited as implied by the complainant. The use of data, be it published or otherwise, to promote an unlicensed product or indication was prohibited by the Code, however the legitimate exchange of medical and scientific information was allowed in limited circumstances.

The Panel noted that as submitted by Pharmacosmos the new data from clinical trials to be discussed at the symposium was about Monofer, however that was not stated or implied anywhere on the flyer. The flyer referred to single high dose intravenous iron in IBD patients. The Panel noted that Monofer and, in limited circumstances CosmoFer, could be administered as a single total dose infusion. The Panel considered that the flyer did not directly or indirectly refer to either medicine and thus was not promotional as implied by the complainant. The requirement to include prescribing information did not apply and no breach of the Code was ruled. As a consequence of its finding that the flyer was not promotional the Panel made other rulings of no breach of the Code.

An anonymous, non-contactable complainant who described themselves as a health professional complained about a double sided, A5 invitation to a Pharmacosmos symposium at the 8th Congress of ECCO (European Crohn's and Colitis Organisation) to take place in 14-16 February 2013. The invitation asked 'Can we optimize treatment with single high dose intravenous iron in IBD [inflammatory bowel disease] patients? – *New data from clinical trials*'. Pharmacosmos marketed Monofer (iron as iron (III) isomaltoside 100) and CosmoFer (iron dextran)). Both products were for the intravenous treatment of iron deficiency and both could be administered as total dose infusions.

COMPLAINT

The complainant stated that he/she had just transferred to a London hospital and the invitation was in the department. However, the material was supposed to be new and therefore the complainant did not understand how it could be discussed or promoted until published and licensed.

When writing to Pharmacosmos A/S, the Authority asked it to respond in relation to Clauses 3.1, 3.2, 4.1, 9.1 and 2 of the Code.

RESPONSE

Pharmacosmos stated that as the complaint was both anonymous and general, it was difficult to investigate any specific aspect of the matter. The complaint did not specify which aspect of the invitation gave cause for concern, other than that the data might not be within the product licence. Since the invitation did not identify a specific product in any capacity, it was not practical for the reader to identify a product licence against which the comments should be made.

Pharmacosmos submitted that twenty of the approved symposium flyers were given to each of its UK representatives in early October following its UK sales conference. Pharmacosmos would attend the ECCO conference. The Pharmacosmos symposium was open to all conference attendees it was an official part of the agenda and as such was a legitimate occasion for scientific exchange regarding treatments and products. Information about the symposium and all industry symposia was available from the conference organizer's website. Pharmacosmos noted that Clauses 3.1 and 3.2 related to promotional activity (or activity that was deemed to be promotional).

The purpose of the flyer was to inform physicians attending the conference that Pharmacosmos would hold a scientific symposium at the conference. There was no intention to distribute the flyer more widely and so Pharmacosmos had not regarded this as a promotional piece *per se*. There was no reference on the flyer to a *specific* product and no mention of any product name. While Pharmacosmos recognised these were not the only determinants of promotion, these were key considerations when reviewing this item in combination with the intention that it would only be given to health professionals known to be attending ECCO. Indeed, there would be little value in providing the flyer to those who would not attend ECCO because the symposium was part of the main conference and could not be attended by any physician who was not registered for the conference. It was unclear how the flyer ended up on a hospital department noticeboard; Pharmacosmos assumed it was placed there by a well-meaning colleague of the complainant.

Pharmacosmos submitted that there was nothing in the title of the symposium, 'Can we optimise treatment with single high dose intravenous iron in IBD patients? – *New data from clinical trials*', which would indicate use of any particular product. Pharmacosmos noted that Monofer was already licensed for high dose intravenous use in IBD and that the presentation was intended to be about Monofer data. However, Monofer and its licence status were not directly identifiable from the flyer.

Pharmacosmos submitted that as the complaint had been received six weeks before the symposium was due to be held the presentations were not written and thus had not been submitted to Pharmacosmos for review. However, a copy of the symposium agenda was provided. Neither the agenda nor any other material about the symposium had been given to any UK health professionals.

Given all the circumstances, Pharmacosmos denied breaches of Clauses 3.1 and 3.2.

Pharmacosmos and other companies made a number of products related to intravenous iron therapy, the majority of which were suitable for use in patients with IBD. On that basis Pharmacosmos stated that the invitation did not identify any specific product. Pharmacosmos would not normally add obligatory information to meetings invitations unless the invitation text specifically named or indicated a specific product. An Appeal Board ruling had made it clear that a reference to a class of treatment was not promotional *per se* unless a specific treatment was identifiable (Case AUTH/2482/2/12).

Given that the material did not promote a specific medicine, there was no requirement for prescribing information to be included. Pharmacosmos thus denied a breach of Clause 4.1.

Pharmacosmos was grateful that the concerns had been raised and for the opportunity to comment; further it denied breaching Clauses 2, and 9.1 of the Code.

PANEL RULING

The Panel noted that the front page of the 2 page flyer featured a headline banner which read 'Invitation'. The reader was then invited to save the date for the Pharmacosmos symposium followed by the statement 'Can we optimize treatment with single high dose intravenous iron in IBD patients? - *New data from clinical trials.*' The background picture was of someone adjusting the flow of an intravenous drip. The reverse featured similar details about the date, time and location of the symposium above corporate information about Pharmacosmos and referred to treatment options with maximum efficacy, convenience and safety for patients and professionals. Readers were invited to visit the corporate website for more information.

The complainant's concern was that new material could not be discussed or promoted until it was published or licensed and in this regard the Panel noted that it was confined to considering the content of the flyer. The Panel noted that discussion or promotion of medicines based on unpublished clinical data was not universally prohibited as implied by the complainant. The use of data, be it published or otherwise, to promote an unlicensed product or indication was prohibited by Clauses 3.1 and 3.2, however the discussion of such data might be permitted in those limited circumstances set out in the supplementary information to Clause 3, Marketing Authorisation, regarding the legitimate exchange of medical and scientific information.

The Panel queried whether the flyer had been distributed solely to physicians attending the conference as submitted by Pharmacosmos. The target audience on the relevant job bag form was described simply as 'gastro clinicians' and each UK representatives had been provided with twenty although the Panel did not know how they were briefed to use them and how many had been distributed.

The Panel firstly had to decide whether the flyer was promotional. The Panel noted that as submitted by Pharmacosmos the new data from clinical trials to be discussed at the symposium was about Monofer, however that was not stated or implied anywhere on the flyer. The flyer referred to single high dose intravenous iron in IBD patients. The Panel noted that, in limited circumstances, both Monofer and CosmoFer could be administered as a single total dose infusion. The Panel considered that the flyer did not directly or indirectly refer to either medicine and was thus not promotional Monofer as implied by the complainant. The requirement to include prescribing information did not apply and thus no breach of Clause 4.1 was ruled. Noting its finding that the flyer was not promotional the Panel also ruled no breach of Clauses 3.1 and 3.2. The Panel consequently ruled no breach of Clauses 2 and 9.1.

Complaint received **20 December 2012**

Case completed **6 February 2013**

CASE AUTH/2577/2/13

VOLUNTARY ADMISSION BY ABBVIE

Out-of-date prescribing information

Abbvie voluntarily admitted that out-of-date prescribing information had been linked to an online Humira (adalimumab) banner advertisement and included in a hard copy Humira journal advertisement. The materials at issue, which were published in December 2012, promoted Humira for the treatment of moderate to severe, active rheumatoid arthritis.

The detailed response from Abbvie is given below.

The Panel noted that as the banner advertisement had appeared on a UK website and the journal advertisement had been published in international journals which were based in the UK, they both came within the scope of the Code. Although the material had been placed by Abbvie's global group, it was a well established principle under the Code that UK companies were responsible for the acts or omissions of overseas parents or affiliates that came within the scope of the Code.

The Code stated that the prescribing information consisted of, *inter alia*, a succinct statement of common side-effects likely to be encountered in clinical practice, serious side-effects and precautions and contra-indications relevant to the indications in the advertisement. The Panel noted that the prescribing information at issue was last revised in May 2011 and did not include two common side-effects and two serious, uncommon side-effects of Humira that were included in the December 2012 prescribing information. The Panel considered that as the prescribing information linked to the banner advertisement and included in the journal advertisements was not up-to-date with regard to precautions and side-effects it did not comply with the Code. High standards had not been maintained. Breaches of the Code were ruled.

Abbvie Ltd voluntarily admitted that out-of-date prescribing information had been linked to an online Humira (adalimumab) advertisement (ref AXHUR111644a) and included in a hard copy Humira advertisement (ref AXHUR111644) which was published in four journals. The material at issue promoted Humira for the treatment of moderate to severe, active rheumatoid arthritis.

As Paragraph 5.6 of the Constitution and Procedure required the Director to treat a voluntary admission as a complaint, the matter was taken up with Abbvie.

COMPLAINT

Abbvie submitted that it had become aware of a potential breach of the Code and drew attention to an online banner advertisement for Humira placed on rheumatology.org.uk on 17 December 2012 by the global rheumatology team. The advertisement had been approved by the UK affiliate in October 2011. On inspection it became clear that the linked prescribing information was now out-of-date (ie version 23) contrary to Clause 4.2 of the Code.

Abbvie contacted the publisher and requested the immediate removal of the banner advertisement. The advertisement was taken down within an hour of Abbvie knowing about the breach. Abbvie also contact the advertising agencies involved and its global colleagues. Both confirmed that there was no other online advertising using the same out-of-date prescribing information.

In the course of these communications, Abbvie also became aware that on 17 December 2012 the global rheumatology team had commissioned the printed advertisements. These advertisements had also been approved by the UK affiliate in October 2011, but also now included prescribing information which was out-of-date (version 23). The advertisements were scheduled to appear in Annals of Rheumatic Disease, Rheumatology, International Rheumatology and Clinical Rheumatology. The first two of these journals were based in the UK.

On becoming aware of this, Abbvie requested the print run to be stopped but was unfortunately too late to stop the out-of-date advertisements appearing in the January 2013 editions of the journals, in breach of Clause 4.2. The advertisement had been withdrawn from all future issues.

In summary, Abbvie submitted that it became aware of two incidents where outdated prescribing information was included in an online advertisement and printed journal advertisements for Humira. The online advertisement was withdrawn as a matter of urgency and the printed advertisements had been withdrawn from future issues.

After an investigation, including a review of processes involved, Abbvie believed that this was an isolated incident. The incident was an individual's error, rather than Abbvie processes which were not followed by a new employee. Retraining of the employee was underway.

In terms of further preventative measures, an updated global standard operating procedure (SOP) was in development. This would mandate that global marketing could not make promotional advertisements on behalf of an affiliate, and only an affiliate could make a placement in its local market.

Abbvie considered that there was no risk to patient safety arising from this incident and the correct prescribing would have been available through