CASE AUTH/2581/2/13

BOEHRINGER INGELHEIM AND LILLY v MERCK SHARP & DOHME

Promotion of Januvia

Boehringer Ingelheim and Lilly complained that a Januvia (sitagliptin) leavepiece issued by Merck Sharp and Dohme raised doubts about the efficacy of their medicine Trajenta (linagliptin). Januvia and Trajenta were both indicated for the treatment of type 2 diabetes.

The complainants noted a bar chart which depicted glycaemic data adapted from Gallwitz *et al* (2012), a non-inferiority study to assess the long-term efficacy and safety of linagliptin vs glimepiride (a sulphonylurea). The study demonstrated that linagliptin was non-inferior to glimepiride with regard to glycaemic control. Secondary endpoints of hypoglycaemic events and change in bodyweight were in favour of linagliptin and were key considerations for clinicians.

The complainants alleged that the bar chart did not allow the reader to form a full and balanced opinion of the efficacy of linagliptin vs glimepiride as there was no reference to the secondary endpoints. The complainants further noted that on the page following the bar chart there were several claims for Januvia. The complainants alleged that the bar chart, followed immediately by claims for Januvia would lead the reader to draw indirect comparisons with linagliptin.

The detailed response from Merck Sharp & Dohme is given below.

The Panel noted that the leavepiece was used proactively to distinguish Januvia from linagliptin in those areas where linagliptin represented a significant commercial challenge. Merck Sharp & Dohme stated that the leavepiece was not intended as a comparison between linagliptin and sulphonylurea, but rather linagliptin and sitagliptin. Given the purpose of the leavepiece, the Panel did not consider that the omission of the hypoglycaemia and body weight results from Gallwitz *et al* was unacceptable. No breach of the Code was ruled.

The Panel noted that the only efficacy data presented regarding linagliptin was the bar chart depicting the results of Gallwitz *et al* which showed that at one year linagliptin lowered HbA_{1c} by 0.38% and at two years by 0.16%. The Panel noted that the two year figure was within the non-inferiority margin of 0.35%. Given the purpose of the leavepiece the Panel queried whether Gallwitz *et al*, in isolation, gave an accurate and balanced overview of the efficacy of linagliptin. Studies (other than Gallwitz *et al*) cited in the Trajenta (linagliptin) summary of product characteristics (SPC) referred to reductions in HbA_{1c} compared to placebo ranging from -0.72% after 52 weeks to -0.57% at 18 weeks. The Panel acknowledged that the results from trials cited in the SPC could not be directly compared but nonetheless such data suggested that the reduction in HbA_{1c} that could be expected from the medicine might be more in the region of -0.5-0.6% as opposed to the -0.38% and -0.16% reported by Gallwitz *et al*. The Panel did not consider that the use of Gallwitz *et al*, in isolation, provided a fair and balanced overview of the efficacy of linagliptin. The Panel considered that the bar chart would unfairly raise doubts about the clinical value and efficacy of linagliptin as alleged and was misleading in that regard. Breaches of the Code were ruled.

The Panel noted that the page of the leavepiece which featured the bar chart was followed by a page listing the key selling points of Januvia, one of which was 'Significant HbA_{1c} reductions'. In the Panel's view, given the stated purpose of the leavepiece, the reader would draw an indirect comparison between this claim and the very small reductions in HbA_{1c} depicted for linagliptin in the bar chart on the previous page. The Panel noted its comments above and considered that the comparison between linagliptin and Januvia was thus misleading. A breach of the Code was ruled.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of the Code was ruled.

Boehringer Ingelheim Limited and Eli Lilly and Company Limited complained about the promotion of Januvia (sitagliptin) by Merck Sharp and Dohme Limited. Januvia was a dipeptidyl peptidase 4 (DPP-4) inhibitor. It was indicated for adult type 2 diabetics to improve glycaemic control as monotherapy, dual combination therapy and triple combination therapy in certain patients. Boehringer Ingelheim and Lilly marketed Trajenta (linagliptin), also a DPP-4 inhibitor with similar indications to Januvia.

The material at issue was a leavepiece (ref DIAB-1061227) which Boehringer Ingelheim and Lilly alleged had been in circulation in its current form since November 2012. The first version of the leavepiece appeared in May 2012 and inter-company dialogue, which started in August 2012, led to minor alterations but these fell short of reaching a compromise agreeable to all. The leavepiece was headed 'Januvia – for type 2 diabetes patients uncontrolled on metformin alone'.

The page at issue, page 3, was headed 'Linagliptin vs an SU [sulphonyl urea] (glimepiride) both on top of metformin' followed by the subheading 'With a pre-

specified non-inferiority margin of 0.35%, linagliptin demonstrated non-inferiority vs an SU in reducing HbA_{1c}'. The page featured a bar chart headed 'Mean HbA_{1c} reductions from baseline at 52 weeks and 104 weeks when adding glimepiride 1-4mg or linagliptin 5mg to prior metformin therapy'. The bar chart showed that at 52 weeks the reductions in HbA_{1c} observed with glimepiride and linagliptin were 0.6% and 0.38% respectively. At 104 weeks the reductions were 0.36% and 0.16% respectively.

COMPLAINT

Boehringer Ingelheim and Lilly submitted that the leavepiece was a linagliptin rebuttal/objection-handler. The companies were unclear about the nature of the rebuttal/objections being handled by the leavepiece but were clear that its principal purpose was to raise doubts in the reader's mind about the efficacy of linagliptin and to imply the added benefits of Januvia through the use of indirect comparisons ie in the absence of head-to-head data upon which to make such a comparison. This view was consistent with feedback from both companies' field forces and from clinicians. Boehringer Ingelheim and Lilly alleged breaches of Clauses 7.2, 7.3, and 9.1.

Page 3 of the document included glycaemic data adapted from Gallwitz *et al* (2012) presented as a bar chart. The companies stated that the objective of this non-inferiority study was to assess the long-term efficacy and safety of linagliptin compared with the sulphonylurea glimepiride. The primary end point was change in HbA_{1c} at 2 years; the two main secondary endpoints were hypoglycaemic events and change in body weight.

The study demonstrated that linagliptin was non-inferior to glimepiride with regard to glycaemic control. An adapted representation of the glycaemic endpoints between linagliptin and glimepiride was presented as a bar chart showing the HbA_{1c} changes at 1 and 2 years. The former was an additional secondary endpoint.

The companies alleged that the bar chart did not present the data in a clear, fair, and balanced manner in breach of Clause 7.8 which required that graphs and tables were not included unless they were relevant to the claims or comparisons made. The companies submitted that as the leavepiece was a linagliptin rebuttal/objection-handler it stood to reason that it would be unfairly used to question the clinical value of linagliptin.

Boehringer Ingelheim and Lilly submitted that the data presented did not allow the reader to form a full and balanced opinion of the efficacy and safety of linagliptin compared with glimepiride. In addition to the glycaemic endpoints the study also demonstrated significant benefits of linagliptin treatment vs glimepiride. The key secondary endpoints revealed a 5-fold reduction in hypoglycaemic events and a weight differential of -2.7kg in favour of linagliptin. Reduction in risk of hypoglycaemia and weight gain were key considerations for clinicians treating type 2 diabetes. The companies noted that Clause 7.2 stated, 'Material must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine'. Boehringer Ingelheim and Lilly alleged a breach of Clause 7.2.

In addition, whilst there were several Januvia claims on page 4 of the leavepiece, no Januvia data was presented in the leavepiece to support the claims made.

Boehringer Ingelheim and Lilly alleged that as the exaggerated bar chart was followed immediately by claims of Januvia's efficacy and safety readers would draw indirect comparisons between Januvia and linagliptin.

Boehringer Ingelheim and Lilly submitted that in their view the leavepiece disparaged linagliptin and misled readers and alleged a failure to uphold high standards in breach of Clause 9.1.

RESPONSE

Merck Sharp & Dohme denied that the leavepiece was in breach of Clauses 7.2, 7.3 and 9.1.

Merck Sharp & Dohme submitted that Gallwitz *et al* was the only in-licence study to compare the efficacy of linagliptin with that of an active comparator (a sulphonylurea, the default second-line medicine class after metformin for type 2 diabetes according to current guidelines from the National Institute for health and Clinical Excellence (NICE)). Despite this, and the fact that the data were included in the linagliptin summary of product characteristics (SPC), and that such active comparator trials represented 'gold-standard' evidence for health professionals seeking to make rational prescribing decisions, Boehringer Ingelheim and Lilly had consistently not referred to this study in any of their own promotional materials; they preferred to rely instead on less informative placebo-controlled trials.

Merck Sharp & Dohme stated that the reason for this was self-evident: although the trial nominally demonstrated non-inferiority of linagliptin vs glimepiride, based on a broad non-inferiority criterion of 0.35% relative reduction in HbA_{1c}, the efficacy results obtained with linagliptin were less than impressive. At 52 weeks, the differential HbA_{1c} reduction between the two agents was 0.22% in favour of glimepiride (-0.6% vs -0.38%) and 0.2% at 104 weeks (-0.16% vs -0.36%). Merck Sharp & Dohme believed that most diabetologists would consider these differences to be clinically significant, and the reduction with linagliptin at 104 weeks to be virtually negligible. These results contrasted sharply with those obtained with other DPP-4 inhibitors, particularly (in this context) the trial conducted by Seck *et al* (2010), which demonstrated identical HbA_{1c} reductions of 0.5% between sitagliptin and a sulphonylurea over 2 years.

Merck Sharp & Dohme submitted that Boehringer Ingelheim and Lilly were aware of the significant question marks around the comparative efficacy of linagliptin. The European Public Assessment Report

(EPAR) for linagliptin stated, in relation to Gallwitz *et al* that:

> 'The claim of non-inferior efficacy of linagliptin compared to glimepiride (study 1218.20) [Gallwitz *et al*] is not appropriately supported by data. The pre-defined non-inferiority margin was too wide considering the treatment effects observed for linagliptin as well as glimepiride. In addition, approximately 50% of the patients did not receive the maximum dose of 4mg of glimepiride. Moreover, despite relatively low baseline HbA_{1c} values, more patients in the linagliptin group than in the glimepiride group needed rescue medication (24.7% linagliptin; 21.5% glimepiride) or discontinued the trial due to lack of efficacy (5.8% linagliptin; 1.9% glimepiride). Interestingly, data from the second part of study 1218.50 [a different trial, which investigated the efficacy of linagliptin compared with placebo and glimepiride in patients intolerant to metformin therapy] showed that the treatment with glimepiride induced a mean decrease in HbA_{1c} of 0.82%, whereas linagliptin was associated with a decrease of 0.44%, further supporting the impression that efficacy of the two agents is not similar.'

Furthermore, in Cases AUTH/2440/10/11 and AUTH/2441/10/11 (GP v Boehringer Ingelheim and Lilly) the Panel examined comparative efficacy claims for linagliptin, and concluded:

> 'The Panel considered that the claim at issue implied that Trajenta [linagliptin] offered class-comparable efficacy in all settings, i.e. whether it was used as monotherapy or in combination with other oral hypoglycaemic agents. This did not appear to be so; in all cases where figures were available, the HbA_{1c} lowering effect of Trajenta was less than with other DPP-4 inhibitors … Given the data upon which it was based, the Panel considered that the claim that Trajenta offered 'class-comparable efficacy' was misleading and could not be substantiated. A breach of the Code was ruled. The Panel considered that the statement exaggerated the properties of Trajenta, and a further breach of the Code was ruled.'

Also of interest from the Panel's ruling in the same case was the statement 'The Panel noted that the claim [of class-comparable efficacy] was based on an indirect comparison of efficacy data from various sources'. It would seem that Boehringer Ingelheim and Lilly were content to use indirect comparisons in an attempt to substantiate a blanket efficacy claim (ruled by the Panel to be inadmissible), but were notably more purist about the use of indirect comparisons that were not to linagliptin's advantage. In the absence of head-to-head data, it was not unreasonable to compare the relative efficacy of two products based on their performance in very similar trials, especially where (as noted for linagliptin in the EPAR quotation, above) the efficacy results were similar across different studies.

Merck Sharp & Dohme referred to the protracted inter-company dialogue about the leavepiece which led it to believe that it could not have made any change to the bar chart which would have satisfied Boehringer Ingelheim and Lilly, short of removing it. Therefore, it appeared that the inter-company dialogue process was futile from its inception and the true purpose of the companies was to suppress any dissemination of the data from this pivotal trial. Merck Sharp & Dohme believed that prescribers should be able to draw their own conclusions as to the value and significance of Gallwitz *et al*.

Merck Sharp & Dohme submitted that it had never denied that the leavepiece was developed as a linagliptin rebuttal/objection-handler. As such, the comparative efficacy of linagliptin was a valid subject for discussion, and Merck Sharp & Dohme did not understand Boehringer Ingelheim and Lilly's assertion that a pivotal linagliptin efficacy trial, the only available study in which an active comparator was employed, would not be relevant.

Merck Sharp & Dohme saw no need to include every detail of Gallwitz *et al* in the leavepiece, including the safety and tolerability profile of linagliptin. It was well accepted that DPP-4 inhibitors exhibited low risks of hypoglycaemia and weight gain. The leavepiece was not intended as a comparison between linagliptin and sulphonylurea, but rather linagliptin and sitagliptin. It was ironic that Boehringer Ingelheim and Lilly should quote the provisions of Clause 7.2 on this point, as Merck Sharp & Dohme believed that the omission of Gallwitz *et al* from their own materials rendered them insufficiently complete to enable recipients to form their own opinion of the therapeutic value of linagliptin.

Merck Sharp & Dohme submitted that all the Januvia claims in the leavepiece were referenced and substantiable. As such, there was no requirement under the Code to include detailed Januvia data, particularly in a piece developed for a very specific purpose and not intended as a general Januvia detail aid.

The issue of indirect comparisons was referred to above. In the absence of head-to-head studies of efficacy and safety between any two medicines in the same class, prescriber choice would inevitably depend on some form of indirect comparison. The point at issue in this case was whether prescribers should be enabled to have access to all relevant data in order to inform their treatment decisions as fully as possible.

Merck Sharp & Dohme submitted that it had been fair in representing the Gallwitz *et al* data and ensured that recipients of the leavepiece were provided with the necessary information to make an informed decision. The fact that Boehringer Ingelheim and Lilly considered a fair representation of data with their own product to be 'disparaging' was telling in itself.

In conclusion, the use of rebuttal/objection-handlers was well-established in the pharmaceutical industry. The representatives' briefing material for the original version of the leavepiece made it clear that the leavepiece was not intended for general

use, but only for well-defined linagliptin 'hotspot' areas, ie areas in which linagliptin represented a significant commercial challenge. As such, data on the comparative efficacy of linagliptin was highly relevant. Furthermore, the leavepiece had not been made generally available to representatives – a specific written request had to be made to the brand management team, outlining the reasons for use.

Merck Sharp & Dohme submitted that it had not 'cherry-picked' Gallwitz *et al* – it was the only trial in which linagliptin was compared with an active comparator (indeed the active comparator given that sulphonylureas were the default second-line medication class according to NICE guidelines). As such, Gallwitz *et al* was the most informative available study on the comparative efficacy of linagliptin. The current version of the leavepiece was fair in representing these efficacy data. Although Merck Sharp & Dohme agreed with the EPAR assessment that the pre-specified, non-inferiority criterion in Gallwitz *et al* was drawn so broadly as to be practically meaningless, it had nevertheless noted in bold typeface that linagliptin was non-inferior above the bar chart at issue, and the non-inferiority margin was also specified below the chart. In addition, the briefing material made it quite clear that, when discussing the study, if doubts were raised about the efficacy of linagliptin, the representative was obliged to state the non-inferiority finding.

Merck Sharp & Dohme believed that it had acted in good faith throughout the inter-company dialogue process, and had made every effort to accommodate Boehringer Ingelheim and Lilly's concerns. It regretted that this matter had been referred to the PMCPA, but it appeared that nothing it could have done would have satisfied Boehringer Ingelheim and Lilly other than removal of any reference to Gallwitz *et al*.

PANEL RULING

The Panel noted that the leavepiece at issue (ref DIAB-1061227) had been superseded in January 2013 by closely similar material (ref DIAB-1067466) which addressed some of the concerns raised in inter-company dialogue.

The Panel noted Boehringer Ingelheim and Lilly's remaining concern that the leavepiece would raise doubts in the reader's mind about the efficacy of linagliptin. The companies had further noted that the Code stated that 'material must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine'. The Panel noted that although that quotation from the Code appeared to relate to what a company stated about its own medicine, the same was true for what a company stated about its competitor.

The Panel noted that the leavepiece was to be used in well-defined linagliptin 'hot spots' ie in areas where linagliptin represented a significant commercial challenge. As such, Merck Sharp & Dohme had submitted that data on the comparative efficacy of linagliptin was highly relevant. The representatives' briefing material stated that the leavepiece was to be used proactively to distinguish Januvia and Janumet (sitagliptin/metformin combination) from linagliptin. Merck Sharp & Dohme had also stated that the leavepiece was not intended as a comparison between linagliptin and sulphonylurea, but rather linagliptin and sitagliptin. Given the purpose of the leavepiece, the Panel did not consider that the omission of the hypoglycaemia and body weight results from Gallwitz *et al* which compared linagliptin and glimepiride was unacceptable. No breach of Clause 7.8 was ruled.

The Panel noted that the only efficacy data presented regarding linagliptin was the bar chart depicting the results of Gallwitz *et al* which showed that at one year linagliptin lowered HbA_{1c} by 0.38% and at two years by 0.16%. The Panel noted that the two year figure was within the non-inferiority margin of 0.35%. The Panel noted the purpose of the leavepiece ie to compare the efficacy of linagliptin with that of sitagliptin and it queried whether Gallwitz *et al*, in isolation, gave an accurate and balanced overview of the efficacy of linagliptin. Studies (other than Gallwitz *et al*) cited in Section 5.1 of the Trajenta (linagliptin) SPC referred to reductions in HbA_{1c} compared to placebo ranging from -0.72% after 52 weeks (in patients with severe renal impairment with linagliptin as monotherapy) to -0.57% at 18 weeks (linagliptin as monotherapy). In that regard the Panel queried whether the results of Gallwitz *et al* were outliers ie a reduction of 0.16% at 2 years. The Panel acknowledged that the results from all of the trials cited in the Trajenta SPC could not be directly compared but nonetheless such data suggested that the reduction in HbA_{1c} that could be expected from the medicine might be more in the region of -0.5-0.6% as opposed to the -0.38% and -0.16% reported by Gallwitz *et al*. The Panel did not consider that the use of Gallwitz *et al*, in isolation, provided a fair and balanced overview of the efficacy of linagliptin. In the Panel's view, readers would see the figures of -0.38% and -0.16% and assume that was the standard HbA_{1c} lowering effect of linagliptin which was not so. Merck Sharp & Dohme had stated that it believed that most diabetologists would consider the HbA_{1c} reduction with linagliptin at 104 weeks to be virtually negligible. The Panel considered that the bar chart would unfairly raise doubts about the clinical value and efficacy of linagliptin as alleged and was misleading in that regard. A breach of Clause 7.2 was ruled. The Panel did not consider that the bar chart gave a clear, fair and balanced view of the efficacy of linagliptin. A breach of Clause 7.8 was ruled.

The Panel noted that the page of the leavepiece which featured the bar chart was followed by a page listing the key selling points of Januvia. The Panel noted the complainants' concern that no data was presented in the leavepiece to support the claims made. In that regard the Panel noted that substantiating data did not have to be presented in promotional material but that all claims had to be capable of substantiation. There was no allegation that the claims could not be substantiated and the Panel further noted that all of the claims were referenced and a list of references was included.

One of the key selling points listed was 'Significant HbA_{1c} reductions'. In the Panel's view, given the stated purpose of the leavepiece, the reader would draw an indirect comparison between this claim and the very small reductions in HbA_{1c} depicted for linagliptin in the bar chart on the previous page. The Panel noted its comments above about the data depicted in the bar chart and considered that the comparison between linagliptin and Januvia was thus misleading. A breach of Clause 7.3 was ruled.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

Complaint received **28 February 2013**

Case completed **15 April 2013**
