# GENERAL PRACTITIONER v BOEHRINGER INGELHEIM and LILLY

## Promotion of Trajenta

**A general practitioner complained about a Trajenta (linagliptin) leavepiece entitled 'Control and care matter'. Trajenta was co-marketed by Boehringer Ingelheim and Lilly for the treatment of type 2 diabetes mellitus to improve glycaemic control in adults. It could be used as monotherapy or combination therapy.**

**The complainant alleged that the campaign to sell Trajenta as a DPP-4 [dipeptidyl peptidase 4] inhibitor that was 'different' from others in the class relied on misleading, unbalanced/selective, unsubstantiable and grossly exaggerated/distorted material. The complainant noted that the headline across pages 2 and 3 of the leavepiece was 'Glycaemic control … with a difference …'. Page 3 featured a list of various differences which were wholly or partially incorrect with reference to the headline which invited a direct comparison with the other DPP-4 inhibitors referred to in the leavepiece.**

**The complainant submitted that, compared with saxagliptin the only valid differences were that: Trajenta was the first DPP-4 inhibitor primarily excreted via the bile; that 5% of the Trajenta dose was excreted via the kidney and that no dosage adjustment was required for patients with hepatic impairment.**

**The complainant alleged that in the management of type 2 diabetics with renal impairment, Trajenta was not different or the first DPP-4 inhibitor, as implied; saxagliptin could also be used with no dose adjustment in mild renal impairment. Trajenta could only claim to be different from saxagliptin with regard to its use specifically in patients with moderate and severe renal impairment where no dose adjustment was necessary; to suggest saxagliptin could never be used without dosage adjustment was misleading, exaggerated and endangered patient safety.**

**The claim that no additional treatment-related renal monitoring was required with Trajenta was alleged to be misleading and potentially dangerous. This might be the case when Trajenta was used as a monotherapy but not so when used in combination with metformin, in this regard the National Institute for Health and Clinical Excellence (NICE) guidelines advocated regular renal monitoring of patients with type 2 diabetes as a required aspect of good clinical practice; to suggest otherwise for the use of Trajenta (even in monotherapy) was irresponsible.**

**The leavepiece suggested that Trajenta was appropriate in adult patients with type 2 diabetes at high risk of declining renal function. The complainant questioned how this squared with the claim that such patients could be managed with Trajenta without the need for additional treatment-related renal monitoring. The placement of the claim that Trajenta was appropriate in adult patients with type 2 diabetes at high risk of declining renal function, under the banner of glycaemic control with a difference, also suggested that Trajenta was different to the other DPP-4 inhibitors; this was not so as all DPP-4 inhibitors could be used to treat these patients.**

**The headline 'Glycaemic control … with a difference …' also suggested that Trajenta had been specifically licensed for indications that were somehow different from the other DPP-4 inhibitors.**

**The complainant alleged that the way in which the above information was laid out under the banner of 'Glycaemic control … with a difference…', suggested that the glycaemic control offered by Trajenta (ie reductions in $HbA_{1c}$ vs placebo) was somehow directly, solely and causally related to the mode of excretion in bile, no requirement to adjust dosages or renal/hepatic monitoring; this could not be substantiated.**

**The complainant submitted that the leavepiece also stated that Trajenta was different from the other DPP-4 inhibitors in that it was the first one dose, once daily DPP-4 inhibitor excreted primarily via the bile: no dose adjustment required. This claim was general, all encompassing and misleading given that saxagliptin was also a once-daily medicine which did not require dose adjustment in mild renal impairment. Trajenta was also not different with regard to the implied claim that it only could be taken with or without food.**

**The complainant stated that as there were no published, randomized, controlled trials comparing the safety and efficacy of Trajenta with sitagliptin, vildagliptin and saxagliptin the claim 'Glycaemic control… with a difference…' could not be substantiated. It appeared that the emphasis of the leavepiece was to specifically compare only those aspects of the summaries of product characteristics (SPCs) relating to dosing requirements according to renal impairment, but even this had been deliberately misrepresented with respect to saxagliptin and its use in mild renal impairment! This comparison of the SPCs was selective and unbalanced with regard to facilitating a proper and full consideration of the comparative risk/benefit profile. The expediency of this omission became more apparent when on a previous page Trajenta was described as being generally well tolerated with an overall incidence of adverse events similar to that of placebo. If a direct comparison was being invited with the other DPP-4**

**inhibitors then a balanced and accurate comparison of the adverse event profile of all the medicines referred to should have been provided. Comparison of the warnings and precautions of the medicines mentioned was also clinically relevant and a serious omission. The selective use of regulatory documents such as SPCs to support a misleading promotional campaign was unacceptable.**

**The detailed response from Lilly and Boehringer Ingelheim is given below.**

**The Panel noted that the leavepiece was entitled 'Control and care matter'. The front cover set out the licensed indications for the product. The next three pages, ie the three page spread when the leavepiece was opened were headed 'Glycaemic control …', '… with a difference …' and 'Trajenta' respectively and set out various features of the medicine. The fifth page carried the prescribing information and the back page of the leavepiece featured a table comparing dosage recommendations of the currently available DPP-4 inhibitors according to degree of renal impairment.**

**The centre inside page, headed '… with a difference …', stated that Trajenta was the first DPP-4 inhibitor excreted primarily via the bile. The Panel did not consider that the claim implied that Trajenta was the first DPP-4 inhibitor as alleged. Health professionals would understand from the claim that Trajenta was the first in its class to be excreted primarily via the bile. No breach of the Code was ruled.**

**The claim relating to biliary excretion was followed by four bullet points each of which referred to a particular feature of Trajenta. The first bullet point stated '5% of the Trajenta dose is excreted via the kidney'. The second bullet point stated 'No dose adjustment'. In that regard Trajenta was different, as implied by the page heading, as the dose of all of the other DPP-4 inhibitors had to be adjusted in certain patient populations, for example those with declining renal functions. The Panel considered that the unqualified claim 'No dose adjustment' for Trajenta was not misleading and that it could be substantiated. No breach of the Code were ruled. The Panel did not consider that the claim suggested that saxagliptin could never be used without dose adjustment as alleged. In that regard the claim was neither misleading nor exaggerated. No breach of the Code was ruled. This was upheld by the Appeal Board following an appeal from the complainant. The Panel did not consider that the claim endangered patient safety as alleged. No breach of the Code was ruled.**

**The third bullet point stated 'No additional treatment-related renal monitoring required'. The Panel considered that this claim could be substantiated as the SPC clearly stated that 'For patients with renal impairment, no dose adjustment for Trajenta is required'. The Panel noted that NICE guidance on the management of type 2 diabetes stated that, regardless of the presence of nephropathy, kidney function should be measured annually. The Panel did not consider that the claim as issue suggested that regular monitoring should not be carried out. There was no additional monitoring to be done as a consequence of initiating Trajenta therapy. The Panel did not consider that the claim was misleading or that it was potentially dangerous as alleged. In the Panel's view the claim was not such that it did not encourage the rational use of Trajenta. No breach of the Code was ruled.**

**Below these bullet points and in a different font colour (orange) and type, was the sub-heading 'Appropriate for adult patients with type 2 diabetes at high risk of declining renal function'. The Panel considered that the presentation of the claim at issue was unlike the bullet points above which clearly related to differences between Trajenta and other DPP-4 inhibitors. The claim now at issue related to how Trajenta could be used. The Panel noted that Trajenta was the only available DPP-4 inhibitor which could be administered without any change in the dose to patients with any degree of renal failure. All the DPP-4 inhibitors could be used in patients at high risk of declining renal function. If patients were at high risk of declining renal function then once they had at least moderate renal failure sitagliptin and vildagliptin were no longer recommended. The dose of saxagliptin had to be reduced in moderate renal failure and used with caution in severe renal impairment. The Panel considered that as a product benefit of Trajenta the combination of the claim with a difference and the sub-heading was not unacceptable as alleged. If a patient was at high risk of declining renal function then it did not seem inappropriate, if a DPP-4 inhibitor was considered suitable, for that DPP-4 inhibitor to be Trajenta given the restrictions for use of the other DPP-4 inhibitors in renal impairment. No breach of the Code was ruled.**

**The sub-heading was followed by two further bullet points, 'Prescribe Trajenta 5mg once daily' and 'Can be taken with or without food'. The Panel noted the page heading '… with a difference …' and that all other DPP-4 inhibitors could be taken with or without food. Although in that regard Trajenta was no different from the other DPP-4 inhibitors the Panel considered that the page layout and presentation of the data was such that the lower half of the page would be seen as setting out the practical details for the prescribing of Trajenta in patients at high risk of declining renal function, ie 5mg once daily, with or without food. The Panel acknowledged that the page heading was '… with a difference ….' but considered that on balance given its positioning the claim 'Can be taken with or without food' was not misleading as alleged. No breach of the Code was ruled. This was upheld by the Appeal Board following an appeal from the complainant.**

**The Panel noted that health professionals would know to assess renal function before prescribing metformin and at least annually thereafter. As a result, the Panel did not consider that the claim 'No additional treatment-related renal monitoring required' suggested that such monitoring should not continue – only that the addition of Trajenta to metformin therapy would not necessitate additional monitoring. The Panel did not consider that the claim was misleading or potentially dangerous as alleged. No breach of the Code was ruled.**

**The Panel did not consider that given the absence of any information about the indications for the other DPP-4 inhibitors, the headline 'Glycaemic control… with a difference …' suggested that Trajenta had been specifically licensed for indications which were different to the other medicines, ie for the treatment of type 2 diabetes. The Panel did not consider that the leavepiece was misleading in that regard. No breach of the Code was ruled.**

**The Panel further did not consider that the presentation of the data suggested that the glycaemic control observed with Trajenta was somehow directly, solely or causally related to its route of excretion or the fact that no dosage adjustments were required in renal or hepatic failure. The Panel thus did not consider that the leavepiece was misleading in that regard. No breach of the Code was ruled.**

**The third inside page, ie the extreme right hand page of the leavepiece when opened out, was headed 'Trajenta' and included the claim 'Different – the first one dose, once daily DPP-4 inhibitor excreted primarily via the bile: no dose adjustment required'. The Panel noted, as above, that Trajenta was the first in class to be excreted primarily by the bile and to need no dose adjustment in any patient group. In that regard the Panel considered that the claim was not misleading or exaggerated. No breach of the Code was ruled.**

**The Panel noted that the leavepiece provided health professionals with a short introduction to Trajenta; it briefly described its efficacy vs placebo, set out practical consideration for its use (no dose adjustment or additional treatment-related renal monitoring) and stated the incidence of adverse events vs placebo. The back page featured a table detailing the dosage recommendations of currently available DPP-4 inhibitors according to the degree of renal impairment. The Panel noted that the data given in the table for saxagliptin was consistent with the particulars listed in the Onglyza SPC. The leavepiece did not purport to be a comprehensive comparison of Trajenta vs all of the other DPP-4 inhibitors. The Panel considered that the claim regarding the tolerability of Trajenta, 'Generally well tolerated – Trajenta, studied in over 4000 patients in clinical trials, has an overall incidence of adverse events that is similar to placebo' could be substantiated by the SPC to which it was referenced. The Panel did not consider that the omission of a full comparison of the SPCs for all the DPP-4 inhibitors meant that the leavepiece was unbalanced as alleged. The Panel did not consider that data from SPCs had been presented in an unacceptable way and in that regard the leavepiece was not misleading. No breach of the Code was ruled.**

**The Panel noted its rulings above and considered that neither Boehringer Ingelheim nor Lilly had failed to maintain high standards. No breach of the Code was ruled. This ruling was upheld by the Appeal Board following an appeal from the complainant. The Panel also did not consider that either company had brought discredit upon, or reduced confidence in, the pharmaceutical industry. No breach of Clause 2 was ruled.**

A general practitioner complained about a six page, gate-folded Trajenta (linagliptin) leavepiece entitled 'Control and care matter' (ref UK/TJR/00031). Trajenta was co-marketed by Boehringer Ingelheim Limited and Eli Lilly and Company Ltd for the treatment of type 2 diabetes mellitus to improve glycaemic control in adults. It could be used as monotherapy or combination therapy.

**COMPLAINT**

The complainant alleged that the campaign by Boehringer Ingelheim and Lilly to sell Trajenta as a DPP-4 [dipeptidyl peptidase 4] inhibitor that was 'different' from others in the class appeared to rely on presenting promotional information that was variously misleading, unbalanced/selective, unsubstantiable and grossly exaggerated/distorted.

The complainant noted that the headline across pages 2 and 3 of the leavepiece at issue was 'Glycaemic control … with a difference …'. Page 3 featured a list of various differences which were wholly or partially incorrect with reference to the headline which invited a direct comparison with the other DPP-4 inhibitors referred to in the leavepiece.

The complainant submitted that, compared with medicines such as saxagliptin (Onglyza, co-marketed by Bristol-Myers Squibb and AstraZeneca) the only valid differences were that Trajenta: was the first DPP-4 inhibitor primarily excreted via the bile; that 5% of the Trajenta dose was excreted via the kidney and that no dosage adjustment was required for patients with hepatic impairment.

The complainant alleged that in the management of type 2 diabetics with renal impairment, Trajenta was not different or the first DPP-4 inhibitor, as was implied by the reference to no dose adjustment and no additional treatment-related renal monitoring required. Medicines such as saxagliptin could also be used with no dose adjustment in mild renal impairment. Trajenta could only claim to be different from saxagliptin with regard to its use specifically in patients with moderate and severe renal impairment where no dose adjustment was necessary; to suggest saxagliptin could never be used without dosage adjustment was misleading and exaggerated the facts and endangered patient safety.

The complainant alleged that the claim that no additional treatment-related renal monitoring was required with Trajenta was also misleading and potentially dangerous. This might be so when Trajenta was used as a monotherapy but not when used in combination with metformin; the use of Trajenta in combination with metformin was associated with prescribed schedules for renal monitoring according to guidelines issued by the National Institute for Health and Clinical Excellence (NICE). These guidelines also advocated regular renal monitoring of type 2 diabetics as a required aspect of good clinical practice; to suggest otherwise for the use of Trajenta

(even in monotherapy) was irresponsible.

The complainant noted that the leavepiece suggested that Trajenta was appropriate in adult patients with type 2 diabetes at high risk of declining renal function. If that was the case, how did this square with the claim that such patients could be managed with Trajenta without the need for additional treatment-related renal monitoring? How was the clinician to gauge any decline in renal function when using Trajenta if not by regular renal monitoring? The placement of the claim that Trajenta was appropriate in adult patients with type 2 diabetes at high risk of declining renal function, under the banner of glycaemic control with a difference, also suggested that Trajenta was different to the other DPP-4 inhibitors mentioned in this particular regard; this was not so given that all DPP-4 inhibitors could be used to treat this particular type of patient.

The complainant stated that in the absence of any information about the indication of the DPP-4 inhibitors mentioned, the headline 'Glycaemic control ... with a difference ...' also suggested that Trajenta had been specifically licenced for indications that were somehow different from the other DPP-4 inhibitors listed, ie the treatment of type 2 diabetes.

The complainant alleged that the way in which the above information was laid out, ie under the banner of 'Glycaemic control ... with a difference ...', suggested that the glycaemic control offered by Trajenta (ie reductions in $HbA_{1C}$ vs placebo) was somehow directly, solely and causally related to the mode of excretion in bile, no requirement to adjust dosages or renal/hepatic monitoring; this could not be substantiated.

The complainant submitted that the leavepiece also stated that Trajenta was different from the other DPP-4 inhibitors in that it was the first one dose, once daily DPP-4 inhibitor excreted primarily via the bile: no dose adjustment required. This claim was general, all encompassing and misleading given that saxagliptin was also a once-daily medicine which did not require dose adjustment in mild renal impairment. Trajenta was also not different with regard to the implied claim that it only could be taken with or without food.

The complainant stated that as there were no published, randomized, controlled trials comparing the safety and efficacy of Trajenta with specifically sitagliptin, vildagliptin and saxagliptin the claim 'Glycaemic control ... with a difference ...' could not be substantiated. It appeared that the companies had contrived to specifically compare only those aspects of the summaries of product characteristics (SPCs) relating to dosing requirements according to renal impairment; which was what the commercial emphasis was but as explained above, even this had been deliberately misrepresented in the leavepiece with respect to saxagliptin and its use in mild renal impairment! This comparison of the SPCs was not only selective but was also unbalanced with regard to facilitating a proper and full consideration of the comparative risk/benefit profile as laid out in the full SPCs. The expediency of this omission became more apparent when on a previous page Trajenta was described as being generally well tolerated with an overall incidence of adverse events similar to that of placebo. If a direct comparison was being invited with the other DPP-4 inhibitors then it was incumbent upon the companies to provide a balanced and accurate comparison of the adverse event profile of all the medicines referred to. Comparison of the warnings and precautions of the medicines mentioned was also clinically relevant and a serious omission. The selective cut-and-pasting of regulatory documents such as SPCs in support of a misleading promotional campaign went beyond what was acceptable or desirable.

The complainant stated that given this very deliberate intent to confuse health professionals, the companies might as well have called the medicine 'Tangenta'; a more apt brand name given the questionable basis upon which the difference offered by Trajenta, compared with other DPP-4 inhibitors, was being promoted.

When writing to Boehringer Ingelheim and Lilly, the Authority asked the companies to respond in relation to Clauses 2, 7.2, 7.4, 7.9, 7.10 and 9.1 of the Code.

**RESPONSE**

Boehringer Ingelheim and Lilly submitted a joint response and explained that the leavepiece at issue introduced health professionals to Trajenta. It was used in promotional calls and meetings by primary and secondary care representatives and health service managers in September and was recalled in October during which time approximately 11,000 copies were distributed.

The layout of the item was intended to be read, in order, starting with the front cover, where the approved therapeutic indications for Trajenta were clearly stated, in full, at the first product mention. Page 2 provided the supporting efficacy data in terms of $HbA_{1C}$ reductions vs placebo for the three main indications and ran into page 3 which described Trajenta as a DPP-4 inhibitor, outlined its main features and identified a typical patient in whom Trajenta might be used. Page 4 provided a product summary and reiterated the approved indications and outlined the summary safety information. Page 5 contained prescribing information and references and page 6 featured a table which compared the dose recommendations for DPP-4 inhibitors in renal impairment taken from the SPCs for all DPP-4 inhibitors currently approved for use in the UK.

The companies submitted that the claim 'Glycaemic control ... with a difference' was supported on page 3 by a number of claims. As noted by the complainant, Trajenta had valid differences: the first DPP-4 inhibitor excreted primarily via the bile; only 5% Trajenta dose excreted via the kidney and no dose adjustment for patients with hepatic impairment. Additional differences included no dose adjustment required for patients with any degree of renal impairment (the focus of the chart on page 6) and that no additional monitoring of renal function was necessary as a

consequence. These differences arose from the metabolism, excretion and elimination pathways for Trajenta (excreted largely unchanged with minimal metabolism in the body including hepatic or renal metabolism and eliminated via the faeces through excretion in the bile with only 5% of the administered oral dose excreted via the kidney). This was clearly different from the metabolic and excretory routes of the other DPP-4 inhibitors and allowed Trajenta to be administered as a single 5mg dose without dosage adjustment in any of the special patient populations stated within the SPC. These claims were referenced to the product SPC and other publications supporting pharmacokinetic data for Trajenta which supported the link between Trajenta's unique pharmacokinetic characteristics amongst the DPP-4 inhibitor class and the lack of any requirement for dosage adjustment in special patient populations including renal and hepatic impairment and the elderly.

Boehringer Ingelheim and Lilly considered that the claims were genuine and supportable and not in breach of Clauses 7.2, 7.4, 7.9 and 7.10.

With regard to the claim '.... No additional treatment related renal monitoring required' Boehringer Ingelheim and Lilly submitted that 'additional' used here was intended to refer specifically to any extra monitoring directly consequential on the use of Trajenta; the claim was referenced to the Trajenta SPC. This referred to monitoring in addition to routine monitoring as recommended by NICE, for example, of which none was required. Agents which required any form of dose adjustment as a consequence of decline in renal function would of necessity require monitoring. Annual checks or 'routine care' were not specifically defined and might not be adequate in the clinical setting, particularly in individuals with rapidly declining renal function or who were approaching critical points in terms of specific measurements of renal function, eg estimated glomerular filtration rate (eGFR) 30-45ml/min/1.73m2.

The companies stated that for Trajenta, no additional renal monitoring was required in this situation because there was no need for the dose to be adjusted in mild, moderate or severe renal impairment. This applied to Trajenta only; the companies submitted that they were not suggesting that it was 'not required' for any other medicines used in combination with Trajenta or that 'routine care' renal monitoring could be ignored in terms of general management of patients with type 2 diabetes prescribed Trajenta. The companies agreed that patients with signs of declining renal function needed to be more closely monitored; however, this was independent of, and not a requirement consequent on, their use of Trajenta.

With regard to saxagliptin, the only reference made to prescribing this product in patients with renal impairment was taken directly from Section 4.2 of the Onglyza SPC. The companies submitted that they had neither suggested nor claimed that 'saxagliptin could never be used without dosage adjustment' as alleged.

Boehringer Ingelheim and Lilly submitted that the claim on page 3 (the centre page when the leavepiece was fully opened) '... Appropriate for adult patients with type 2 diabetes at high risk of declining renal function' provided the link between the DPP-4 inhibitor and Trajenta features section above and the Trajenta prescribing section below. When the leavepiece was open, as it would need to be to view this page, the page to the right included the summarised therapeutic indications for Trajenta and which was the next logical section to be read. The therapeutic indications section of the SPC had already been clearly presented on the front cover of the leavepiece. The companies expected that the reader should therefore have gained a good understanding of the therapeutic indications for Trajenta on this basis, having now been exposed to them twice on this single six page item.

The companies agreed that patients for whom the DPP-4 inhibitor class was currently considered appropriate, for example as per NICE guidelines, were advancing in their diabetes and were likely to have signs of declining renal function. The companies submitted that they had not claimed that other DPP-4 inhibitors could not be used in these circumstances but rather that Trajenta could reasonably be used here in the manner in which it had been presented.

Boehringer Ingelheim and Lilly stated that the claim prefaced 'Different' should be read in its entirety, ie 'the first one dose, once daily DPP-4 inhibitor excreted primarily via bile'. Each phrase was not intended to be a stand-alone statement of difference and to do that was to take this out of context.

The companies considered that the comparator table on the back cover was sufficiently balanced as it represented and drew on the publicly available data from the same section of each product SPC for all currently available DPP-4 inhibitors. There were no randomized, controlled trial head-to-head data comparing the efficacy and safety of the various DPP-4 inhibitors currently available in the UK. However, the table aimed to compare dosing recommendations in renal impairment as stated in the header. In the absence of other comparator data, the companies considered a comparison of data in the various product SPCs was the most fair and relevant way to make such comparisons between products in the same treatment class. The wording used was as it appeared in Section 4.2 of each SPC, including the specific wording for use in renally impaired patients. Each product, other than Trajenta, was represented in the same way in terms of font size, colour, shading etc as the companies were not permitted to imply any advantage/disadvantage nor make any claims for any medicine other than their own. The intention was to present the factual data. Boehringer Ingelheim and Lilly submitted that they had included exact wording in the table; where the information was detailed, as was the case for saxagliptin, additional information was included in the footnote so the table was not too text heavy and did not draw attention inappropriately to one particular medicine. Where the detail was not included in the SPC, for example specific measurements or levels of renal impairment other than broad categories, mild,

moderate or severe or reference to creatinine clearance for guidance, the leavepiece did not specify any more than was actually included in the SPC. This was intentional in order to provide a fair and balanced comparison between all product SPCs. The SPCs were the most relevant source of information for conducting a comparison of this nature of the product class and were the acknowledged reference source for information on prescribing in special patient populations and product assessment provided a consistent and highly regulated approach in the manner in which each product was assessed while also allowing the marketing authorization holder to update the information contained in the SPC as and when important new data become available. As stated in the title of the table, this was intended as a comparison of DPP-4 inhibitors for use in renal impairment only and did not purport to compare other features such as the different therapeutic indications for each treatment.

The companies submitted that Trajenta, as outlined above, could be used in patients with mild, moderate or severe renal impairment, irrespective of renal function. Decisions with regard to dose adjustment for any other agents used in combination with Trajenta would be made independently of decisions for Trajenta because different prescribing restrictions pertained for each and would be based on individualised patient assessment.

The companies considered the summary table presented an accurate, clear and balanced view of prescribing the different DPP-4 inhibitors in renal impairment, based on SPC evidence.

The companies stated that on page 4 of the leavepiece, Trajenta was described as 'Generally well tolerated' and this was qualified by wording summarised from Section 4.8 of the SPC which stated 'Trajenta has been evaluated overall in 4,687 patients with type 2 Diabetes Mellitus of which 4,040 received the target dose of 5mg' and 'In the pooled analysis of the placebo-controlled trials, the overall incidence of adverse events in patients treated with placebo was similar to Trajenta 5mg'. In the leavepiece this had been summarised to 'Trajenta, studied in over 4,000 patients in clinical trials has an overall incidence of adverse events that is similar to placebo'. The companies noted that materials for newly licensed products were subject to pre-vetting by the Medicines and Healthcare products Regulatory Authority (MHRA) and the claim 'Generally well tolerated' and text was agreed after feedback from the MHRA as being appropriate as a summary safety statement for a newly licensed DPP-4 inhibitor.

In summary Boehringer Ingelheim and Lilly considered that they had presented Trajenta in an accurate, balanced fair, objective and unambiguous manner based on an up-to-date evaluation of the evidence. They did not intend to mislead by distortion, exaggeration or undue emphasis and preferred to focus on the factual data, all of which was capable of substantiation. The safety data was presented in a clear manner and reflected the SPC as agreed with the MHRA during the pre-vetting process. As such the companies did not consider the leavepiece was in breach of Clauses 7.2, 7.4, 7.9 or 7.10. Boehringer Ingelheim and Lilly submitted that they had maintained high standards in the presentation of the leavepiece and had not undertaken activities or presented materials which brought discredit upon or reduced confidence in the pharmaceutical industry. The companies denied a breach of Clauses 2 or 9.1.

**PANEL RULING**

The Panel noted that the leavepiece was entitled 'Control and care matter'. The front cover set out the licensed indications for the product. The next three pages of the leavepiece ie the three page spread when the leavepiece was opened were headed 'Glycaemic control …', '… with a difference …' and 'Trajenta' respectively and set out various features of the medicine. The fifth page carried the prescribing information and the back page of the leavepiece featured a table comparing dosage recommendations of the currently available DPP-4 inhibitors according to degree of renal impairment.

The centre inside page, headed '… with a difference …', stated that Trajenta was the first DPP-4 inhibitor excreted primarily via the bile. The Panel did not consider that the claim implied that Trajenta was the first DPP-4 inhibitor as alleged. The leavepiece was targeted at health professionals who, in the Panel's view, would understand from the claim that Trajenta was the first in its class to be excreted primarily via the bile. In addition the audience would be aware of the other DPP-4 inhibitors on the market. Details of these were given on the back page of the leavepiece. The Panel did not consider that the claim was misleading. No breach of Clause 7.2 was ruled.

The claim relating to biliary excretion was followed by four bullet points each of which referred to a particular feature of Trajenta. The first bullet point stated '5% of the Trajenta dose is excreted via the kidney'. The second bullet point stated 'No dose adjustment'. In that regard Trajenta was different, as implied by the page heading, as the dose of all of the other DPP-4 inhibitors had to be adjusted in certain patient populations, for example those with declining renal functions. The Panel considered that the unqualified claim 'No dose adjustment' for Trajenta was not misleading and that it could be substantiated. No breach of Clauses 7.2 and 7.4 were ruled. The Panel did not consider that the claim suggested that saxagliptin could never be used without dose adjustment as alleged. In that regard the claim was neither misleading nor exaggerated. No breach of Clauses 7.2 and 7.10 were ruled. This ruling was appealed by the complainant. The Panel did not consider that the claim endangered patient safety as alleged. No breach of Clause 7.9 was ruled. This ruling was not appealed.

The third bullet point stated 'No additional treatment-related renal monitoring required'. The Panel considered that this claim could be substantiated as the SPC clearly stated that 'For patients with renal impairment, no dose adjustment for Trajenta is

required'. The Panel noted that NICE guidance on the management of type 2 diabetes stated that, regardless of the presence of nephropathy, kidney function should be measured annually. The Panel did not consider that the claim as issue suggested that regular monitoring should not be carried out. In the Panel's view health professionals would be well aware of the need to monitor renal function in type 2 diabetes; the claim at issue informed them that there was no additional monitoring to be done as a consequence of initiating Trajenta therapy. The Panel did not consider that the claim was misleading or that it was potentially dangerous as alleged. In the Panel's view the claim was not such that it did not encourage the rational use of Trajenta. No breach of Clauses 7.2 and 7.10 were ruled.

Below these bullet points and in a different font colour (orange) and type, was the sub-heading 'Appropriate for adult patients with type 2 diabetes at high risk of declining renal function'. The Panel considered that the presentation of the claim at issue was unlike the bullet points above which clearly related to differences between Trajenta and other DPP-4 inhibitors. The claim now at issue related to how Trajenta could be used. The Panel noted that Trajenta was the only one of the available DPP-4 inhibitors which could be administered without any change in the dose to patients with any degree of renal failure. All the DPP-4 inhibitors could be used in patients at high risk of declining renal function. If patients were at high risk of declining renal function then once they had at least moderate renal failure sitagliptin and vildagliptin were no longer recommended. The dose of saxagliptin had to be reduced in moderate renal failure and used with caution in severe renal impairment. The Panel considered that as a product benefit of Trajenta the combination of the claim with a difference and the sub-heading was not unacceptable as alleged. If a patient was at high risk of declining renal function then it did not seem inappropriate, if a DPP-4 inhibitor was considered suitable, for that DPP-4 inhibitor to be Trajenta given the restrictions for use of the other DPP-4 inhibitors in renal impairment. No breach of Clause 7.2 was ruled.

The sub-heading was followed by two further bullet points, 'Prescribe Trajenta 5mg once daily' and 'Can be taken with or without food'. The Panel noted the page heading '… with a difference…' and that all other DPP-4 inhibitors could be taken with or without food. Although in that regard Trajenta was no different from the other medicines in the same class, the Panel considered that the page layout and presentation of the data was such that the lower half of the page would be seen as setting out the practical details for the prescribing of Trajenta in patients at high risk of declining renal function ie 5mg once a daily, with or without food. The Panel acknowledged that the page heading was '… with a difference ….'. But considered that on balance given its positioning the claim 'Can be taken with or without food' was not misleading as alleged. No breach of Clause 7.2 was ruled. This ruling was appealed by the complainant.

The Panel noted the complainant's comments about the use of Trajenta in combination with metformin. The Panel noted that metformin was well established in the treatment of type 2 diabetes and so health professionals would be familiar with the need for renal function to be assessed before prescribing and at least annually thereafter. As a result, the Panel did not consider that the claim 'No additional treatment-related renal monitoring required' suggested that such monitoring should not continue – only that the addition of Trajenta to metformin therapy would not necessitate additional monitoring. The Panel did not consider that the claim was misleading or that it was potentially dangerous as alleged. In the Panel's view the claim was not such that it did not encourage the rational use of Trajenta in combination with metformin. No breach of Clauses 7.2 and 7.10 were ruled.

The Panel did not consider that given the absence of any information about the indications for the other DPP-4 inhibitors, the headline 'Glycaemic control… with a difference…' suggested that Trajenta had been specifically licensed for indications which were different to the other medicines, ie for the treatment of type 2 diabetes. The Panel did not consider that the leavepiece was misleading in that regard. No breach of Clause 7.2 was ruled.

The Panel further did not consider that the presentation of the data within the leavepiece suggested that the glycaemic control observed with Trajenta was somehow directly, solely or causally related to its route of excretion or the fact that no dosage adjustments were required in renal or hepatic failure. The Panel thus did not consider that the leavepiece was misleading in that regard. No breach of Clause 7.2 was ruled.

The third inside page, ie the extreme right hand page of the leavepiece when opened out, was headed 'Trajenta' and included the claim 'Different – the first one dose, once daily DPP-4 inhibitor excreted primarily via the bile: no dose adjustment required'. The Panel noted, as above, that Trajenta was the first in class to be excreted primarily by the bile and to need no dose adjustment in any patient group. In that regard the Panel considered that the claim was not misleading or exaggerated. No breach of Clauses 7.2 and 7.10 were ruled.

The Panel noted that the leavepiece provided health professionals with a short introduction to Trajenta; it briefly described its efficacy vs placebo, set out practical consideration for its use (no dose adjustment or additional treatment-related renal monitoring) and stated the incidence of adverse events vs placebo. The back page featured a table detailing the dosage recommendations of currently available DPP-4 inhibitors according to the degree of renal impairment. The Panel noted that the data given in the table for saxagliptin was consistent with the particulars listed in the Onglyza SPC. The leavepiece did not purport to be a comprehensive comparison of Trajenta vs all of the other DPP-4 inhibitors. The Panel considered that the claim regarding the tolerability of Trajenta, 'Generally well tolerated – Trajenta, studied in over 4000 patients in

clinical trials, has an overall incidence of adverse events that is similar to placebo' could be substantiated by the SPC to which it was referenced. The Panel did not consider that the omission of a full comparison of the SPCs for all the DPP-4 inhibitors meant that the leavepiece was unbalanced as alleged. The Panel did not consider that data from SPCs had been presented in an unacceptable way and in that regard the leavepiece was not misleading. No breach of Clause 7.2 was ruled.

The Panel noted its rulings above and considered that neither Boehringer Ingelheim nor Lilly had failed to maintain high standards. No breach of Clause 9.1 was ruled. This ruling was appealed by the complainant. The Panel also did not consider that either company had brought discredit upon, or reduced confidence in, the pharmaceutical industry. No breach of Clause 2 was ruled.

**APPEAL BY THE COMPLAINANT**

The complainant was disappointed that the Panel had considered that the leavepiece in question was faultless. The complainant was inclined to accept this were it not for the fact that the basis for this appeared to be inconsistent.

The complainant stated that on one hand the Panel clearly recognised that some of the claims highlighted features of Trajenta that were different from other DPP-4 inhibitors and ruled this was acceptable and could be substantiated. However, the Panel did not consider that the claim that Trajenta 'Can be taken with or without food', which appeared under the same banner highlighting '… with a difference …' (compared with other DPP-4 inhibitors), was misleading and, evidently, relied on its own subjective criteria of 'balance' rather than the more objective fact that this claim, as presented, was clearly misleading and suggested that Trajenta, unlike other DPP-4 inhibitors, could be taken with or without food.

The complainant stated that whilst in the context of the whole complaint this might seem a relatively minor point, it brought into question the Panel's objectivity in relation to some of the other rulings. The complainant therefore appealed the Panel's ruling of no breach of Clause 7.2.

As the focus of the leavepiece was to highlight differences with other DPP-4 inhibitors, the complainant also appealed the rulings that the leavepiece did not suggest that saxagliptin could never be used without dose adjustment in patients with renal failure. This claim was implicit in the manner in which the information that Trajenta required no dose adjustment was presented early on under the banner of 'difference' but the clarifying details regarding saxagliptin were presented on the last page; it was possible that health professionals might not read the information presented in the SPC comparison on the last page and would therefore be likely to be misled up to that point.

The complainant appealed the ruling of no breach of Clause 9.1 for the above reasons.

**RESPONSE FROM THE BOEHRINGER INGELHEIM and LILLY**

Boehringer Ingelheim and Lilly had no additional comments.

**FINAL COMMENTS FROM THE COMPLAINANT**

The complainant had no additional comments.

**APPEAL BOARD RULING**

The Appeal Board noted that the claim 'No dose adjustment' appeared as a bullet point on the centre inside page, headed '… with a difference …'. The Appeal Board noted that no dosage adjustment of Trajenta was necessary in patients with any degree of renal insufficiency; this was different to other DPP-4 inhibitors, including saxagliptin, as listed on page 6 of the leavepiece. The Appeal Board did not consider that the claim suggested that saxagliptin could never be used without dose adjustment as alleged. In that regard the claim was neither misleading nor exaggerated. The Appeal Board upheld the Panel's ruling of no breach of Clauses 7.2 and 7.10. The appeal on this point was unsuccessful.

The Appeal Board noted that the lower half of the centre inside page was printed in a different font colour (orange) and type face to the top of the page and it started with the subheading 'Appropriate for adult patients with type 2 diabetes at high risk of declining renal function'. Below this subheading there were two bullet points 'Prescribe Trajenta 5mg once daily' followed by the bullet point at issue 'Can be taken with or without food'. The Appeal Board noted that all other DPP-4 inhibitors could be taken with or without food. However, the Appeal Board considered that this bullet point described the practical details for the prescribing of Trajenta, ie that it could be taken with or without food. In the Appeal Board's view, the bullet point would not be read in the context of the heading at the top of the page '… with a difference …'. It considered that the page had been separated into two.

The Appeal Board considered that given its position on the page and the visual differences in colour and typeface the claim 'Can be taken with or without food' was not misleading as alleged. The Appeal Board upheld the Panel's ruling of no breach of Clauses 7.2. The appeal on this point was unsuccessful.

The Appeal Board noted its rulings above and considered that neither Boehringer Ingelheim nor Lilly had failed 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.

**Complaint received** **2 November 2011**

**Case completed** **19 January 2012**