GENERAL PRACTITIONER v BOEHRINGER INGELHEIM and LILLY

Promotion of Trajenta

A general practitioner alleged that the claim that Trajenta offered 'class-comparable efficacy' was misleading and could not be substantiated given that there were no direct head-to-head studies comparing Trajenta with the other medicines in its class (dipeptidyl peptidase-4 (DPP-4) inhibitors). The claim appeared in a press release issued by Boehringer Ingelheim and Lilly.

The detailed responses from Boehringer Ingelheim and Lilly are given below.

The Panel considered, contrary to the complainant's view, that direct head-to-head studies were not necessarily needed to substantiate a claim for 'class-comparable efficacy'. 'Comparable' meant that the two products were worthy of comparison or able to be compared. The Panel did not consider that comparability implied equivalence.

The Panel noted the efficacy tables provided by both companies compared data across the products' respective summaries of product characteristics (SPCs) and detailed the HbA_{1C} lowering effect of Trajenta and the other DPP-4 inhibitors in various clinical settings. For those medicines licensed for use as a monotherapy in patients who could not take metformin the placebo corrected mean change in HbA_{1C} was -0.57% for Trajenta and -0.6%, -0.8% for sitagliptin. When the DPP-4 inhibitors were added to metformin therapy, however, greater differences in efficacy seemed to appear according to SPC data (placebo-corrected mean change in HbA_{1C} was -0.62% Trajenta; -0.7% sitagliptin; -0.8% saxagliptin and -1.1% vildagliptin). Similarly when added to existing therapy with metformin and a sulphonylurea the placebo-corrected mean change in HbA_{1C} was -0.62% with Trajenta and -0.9% with sitagliptin.

The Panel considered that the claim at issue implied that Trajenta offered class-comparable efficacy in all settings, ie 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. The Panel noted that the claim was based on an indirect comparison of efficacy data from various sources; principally from the figures given in the respective SPCs. There was no way of knowing whether the differences were clinically or statistically different. 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 Trajenta and a further breach of the Code was ruled.

A general practitioner complained about a press release (UK/TRJ/00004e) issued by Boehringer Ingelheim Limited and Eli Lilly and Company Limited which had, as a sub-heading, a general comparative efficacy claim for Trajenta (linagliptin) vs other medicines in the same class.

Trajenta was a dipeptidyl peptidase-4 (DPP-4) inhibitor co-marketed by Boehringer Ingelheim and Lilly for the treatment of type 2 diabetes mellitus to improve glycaemic control in adults:

- as monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin was inappropriate due to intolerance, or contraindicated due to renal impairment
- in combination with metformin when diet and exercise plus metformin alone did not provide adequate glycaemic control.
- in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products did not provide adequate glycaemic control.

COMPLAINT

The complainant alleged that the claim that Trajenta was the 'Only DPP-4 inhibitor for use in adults with type 2 diabetes mellitus offering class-comparable efficacy with no requirement for dose adjustment or additional renal monitoring in renal impairment' was misleading and could not be substantiated in the absence of head-to-head comparative studies.

The complainant submitted that it appeared that Trajenta was being promoted by differentiating its use in patients with renal impairment by directly comparing it to other DPP-4 inhibitors. Whilst the latter claim might not need to be based on direct head-to-head comparative studies, surely the broad and sweeping claim that it offered class-comparable efficacy did?

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

RESPONSE

Both companies submitted that the press release was for UK medical media only and timed to coincide with the official UK launch of Trajenta. Boehringer Ingelheim stated that the DPP-4 inhibitor class currently contained four licensed medicines – sitagliptin [marketed as Januvia by Merck, Sharpe & Dohme], saxagliptin [marketed as Onglyza by AstraZeneca], vildagliptin [marketed as Galvus by Novartis] and Trajenta. Each was similar in terms of their efficacy in reducing haemoglobin A_{1C} (HbA_{1C}) in adults with type 2 diabetes. Within the indications for which Trajenta was licensed, the efficacy of this class of medicines was summarised in the table below:

EFFICACY STUDIES	CHARACTERISTICS	Linagliptin (Trajenta)	Sitagliptin (Januvia)		Saxagliptin (Onglyza)			Vildagliptin (Galvus)	
Monotherapy in metformin inappropriate patients	Number	147	193	229	103	69	70	90	79
	Duration (wks)	18/52	18/52	24/52	24/52	24/52	24/52	24/52	24/52
	HbA1c:								
	Baseline	8.1%	8.0%	8.0%	8.0%	8.0%	8.0%	8.6%	8.4%
	Mean change vs. baseline	-0.44%	-0.5%	-0.6%	-0.5%	-0.7%	-0.6%	-0.8%	-0.7%
	Placebo-corrected	-0.57%	-0.6%	-0.8%	-0.6%	-0.4%	-0.4%	-0.5%	-0.7%
Add-on to metformin	Comparators/design				Saxagliptin + Metformin vs.Sitagliptin + Metformin			Vildagliptin + Met vs. Gliclazide + Metformin	
	Number	513	513		801			-	
	Duration (wks)	24	24		18/52			52	
	HbA1c:							Vilda/Gliclazide	
	Baseline	8.0%	8.0%		-			8.4%/8.5%	
	Mean change vs. baseline	-0.49%	-0.49%		-			-0.81%/-0.85%	
	Placebo-corrected	-0.64%	-0.64%		-			-	
	Per protocol analysis	-	-		-0.5%(Saxa), -0.6%(Sita)			-	
	Full analysis set	-	-		-0.4%(Saxa), -0.6%(Sita)			-	
					Saxagliptin non-inferior to Sitagliptin			Vildagliptin non-inferior to Gliclazide	
Add-on to metformin + SU			SU = Glimepiride						
	Number	778	115						
	Duration (wks)	24	-						
	HbA1c:								
	Baseline	8.2%	8.3%						
	Mean change vs. baseline	-0.72%	-0.6%						
	Placebo-corrected	-0.62%	-0.9%						

Both companies submitted that in all of the above indications, the mean placebo-corrected reduction in HbA_{1C} was similar and Boehringer Ingelheim submitted that it was not clinically significantly different across all four medicines in the class and so the efficacy of the DPP-4 inhibitors as a class was worthy of comparison, ie the efficacy of Trajenta and all other DPP-4 inhibitors was comparable. Lilly submitted that the intention of the claim at issue was to reflect similarity and not to imply direct comparisons.

Both companies noted that diabetic nephropathy and renal impairment was a common complication in type 2 diabetes and might range in severity from mild renal impairment to end-stage renal disease. Approximately one third of type 2 diabetics had renal impairment and this might cause clinicians to have to reconsider prescribing decisions for oral hypoglycaemic agents, many of which had restrictions and/or contraindications for use in these patients. All of the DPP-4 inhibitors, except Trajenta, were excreted primarily via the renal route and so in patients with moderate and severe renal impairment they either required dose adjustment and additional renal monitoring prior to use (saxagliptin) or were not recommended (sitagliptin and vildagliptin). Trajenta was the only DPP-4 inhibitor to be excreted primarily unchanged in the bile and so no dose adjustment or additional treatment-related monitoring of renal function was required for its use.

On 19 October, Trajenta became the first and 'Only DPP-4 inhibitor for use in adults with type 2 diabetes mellitus offering class-comparable efficacy with no requirement for dose adjustment or additional renal monitoring in renal impairment'. Both companies therefore denied that Trajenta had been promoted in anything other than an objective and non-exaggerated manner supporting its rational use and it consequently denied a breach of Clause 7.10. Similarly both companies considered that the claim as well as the press release upon which it headlined was accurate, fair, balanced, objective and unambiguous and represented an up-to-date evaluation of all the evidence that supported the use of the DPP-4 inhibitors in adult patients with type 2 diabetes and renal impairment. The companies did not consider that the claim was misleading or distorted, nor did it exaggerate the properties of Trajenta relative to those of the other DPP-4 inhibitors, nor did the claim unduly emphasise the properties or benefits of Trajenta. Consequently a breach of Clause 7.2 was denied. Furthermore, the companies believed the claim in question could be substantiated and they referred to the relevant summaries of product characteristics (SPCs) for the four licensed DPP-4 inhibitors.

Lilly stated that the press release in question was submitted to and approved by the Medicines and Healthcare products Regulatory Authority (MHRA) as part of its pre-vetting process. The claim 'class-comparable efficacy' added to 'no requirement for dose adjustment or additional renal monitoring' appeared only in the press material and had not been used in any promotional materials. To avoid confusion such as that expressed by the complainant, Lilly submitted that it would remove that particular claim from future press releases as well.

PANEL RULING

The Panel noted that Boehringer Ingelheim and Lilly had submitted very similar responses to this complaint, so it considered the cases together.

The Panel noted the complainant's view that direct head-to-head studies were needed to substantiate a claim for 'class-comparable efficacy'. The Panel considered that this was not necessarily so. 'Comparable' meant that the two products were worthy of comparison or able to be compared. The Panel did not consider that comparability implied equivalence.

The Panel noted the efficacy tables provided by both companies compared data across the products' respective SPCs and detailed the placebo-corrected percentage lowering of HbA_{1C} of Trajenta and the other DPP-4 inhibitors in various clinical settings. With regard to the use of those medicines licensed for use as a monotherapy in patients who could not take metformin the placebo corrected

mean change in HbA_{1C} was -0.57% for Trajenta and -0.6%, -0.8% for sitagliptin. When the DPP-4 inhibitors were added to metformin therapy, however, greater differences in efficacy seemed to appear according to data extracted from the relevant SPCs (placebo-corrected mean change in HbA_{1C} was -0.62% Trajenta; -0.7% sitagliptin; -0.8% saxagliptin and -1.1% vildagliptin). Similarly when added to existing therapy with metformin and a sulphonylurea the placebo-corrected mean change in HbA_{1C} was -0.62% with Trajenta and -0.9% with sitagliptin.

The Panel considered that the claim at issue implied that Trajenta offered class-comparable efficacy in all settings, ie 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. The Panel noted that the claim was based on an indirect comparison of efficacy data from various sources; principally from the figures given in the respective SPCs. There was no way of knowing whether the differences were clinically or statistically different. 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 Clauses 7.2 and 7.4 was ruled. The Panel considered that the statement exaggerated the properties of Trajenta and a breach of Clause 7.10 was ruled.

Complaint received **4 October 2011**

Case completed **17 November 2011**