CASE AUTH/2015/7/07

LILLY v BAYER SCHERING PHARMA

Promotion of Levitra

Lilly complained about a journal advertisement and a leavepiece for Levitra (vardenafil) issued by Bayer Schering Pharma. The claim 'Works first time in 9 out of 10 men' appeared in both items referenced to Valiquette *et al* (2005) and qualified, in small print, by 'Successful response rates (SEP2) were clearly demonstrated in the majority of [erectile dysfunction] patients'.

Lilly noted from the study that during the challenge phase, the proportion of patients with a first-time success based on SEP2 was 87%; of these patients, 85% had maintenance of erection (SEP3) sufficient for completion of intercourse, leading to a first-time SEP3 success of 74% of patients. Lilly believed equating 87% success in SEP2 from the challenge phase of this study to 9 out of 10 men achieving successful sexual intercourse with their first vardenafil tablet was an inaccurate and misleading interpretation.

Further, the one week challenge phase was conducted as an open label study; however this was not mentioned in the advertisement nor the leavepiece as an important and clinically relevant study limitation or bias.

The Panel noted that during the open-label challenge phase 520/600 patients given a single dose of Levitra 10mg achieved SEP2 success ie penetration. Although in both the advertisement and the leavepiece a footnote to the claim noted that success was measured as achievement of SEP2, there was no mention that this meant penetration and in any event it was a principle under the Code that claims should not be qualified by the use of footnotes and the like. The Panel considered the impression given by the claim 'Works first time in 9 out of 10 men' was that for 90% of men, their first dose of Levitra resulted in successful intercourse (SEP3) and not just successful penetration (SEP2). This impression was endorsed by the claim 'Get it right first time' in the leavepiece and the strapline 'Right first time' in the advertisement. Further, the data 520/600 did not equate to 9 out of 10. The Panel ruled that the claim was misleading and had not been substantiated in breach of the Code.

Lilly alleged that the claim 'Levitra lets them wine and dine' in the leavepiece referenced to the summary of product characteristics (SPC) was misleading as it was inconsistent with the SPC.

The Panel noted that the SPC stated that Levitra could be taken with or without food and that the onset of activity might be delayed with a high fat meal. The Panel noted that Levitra 20mg did not potentiate the effects of alcohol (mean blood level of 73mg/dl) on blood pressure and heart rate and the pharmacokinetics of Levitra were not altered. The Panel noted that in this regard the blood alcohol limit for driving was 80mg/dl. The Panel considered that given the content of the SPC insufficient information had been given in the leavepiece about the effect of food and drink. In that regard the claim 'Levitra lets them wine and dine' was misleading and a breach of the Code was ruled.

The claim 'Given a choice of PDE5 inhibitors, Levitra is the one many men prefer' appeared in the leavepiece referenced to an abstract presented by Sommer *et al* at a North American congress in 2005. Lilly believed that the Sommer *et al* abstract had not been peer reviewed and noted that the limitations of the study were not stated in the leavepiece; hence the claim of preference was misleading and unfair. Lilly noted that in Case AUTH/1638/10/04 Bayer had been ruled in breach of the Code for using this preference claim from this same study. Lilly alleged that the use of this claim again was a breach of the Code.

The Panel noted that the Sommer abstract provided little information about the design and analysis of the study which compared preferences for vardenafil, sildenafil and tadalafil (Lilly's product Cialis) at maximum and half maximum doses. Levitra had been the preferred treatment at maximum and half maximum doses. At maximum dose 39% of patients preferred Levitra with 22% preferring sildenafil and 38% preferring tadalafil. The corresponding figures at half maximum doses were 44%, 37% and 19%.

The Panel noted the difference in preference expressed for the products. It did not appear that there had been any statistical evaluation of the results. The Panel queried whether a difference of 39% of patients preferring vardenafil compared with 38% preferring tadalafil at maximum approved doses represented a true difference between the two products particularly in the absence of any statistically significant difference. The Panel considered that, based upon the results of Sommer *et al* (2005), the claim was misleading and unfair and breaches of the Code were ruled.

Eli Lilly and Company Limited complained about the promotion of Levitra (vardenafil) by Bayer Schering Pharma. The items at issue were a journal advertisement (ref 7LEVI05) and a leavepiece (ref 7LEVI07). Lilly supplied Cialis (tadalafil).

1 'Works first time in 9 out of 10 men'

This claim appeared in both items and was referenced to Valiquette *et al* (2005). On each piece the claim was qualified, in small print, by 'Successful response rates

(SEP2) were clearly demonstrated in the majority of [erectile dysfunction] patients'.

COMPLAINT

Lilly stated that the efficacy section of Valiquette *et al* stated that during the challenge phase of the study, the proportion of patients with a first-time success based on SEP2 was 87% (520/600 patients); of these patients, 85% had maintenance of erection (SEP3) sufficient for completion of intercourse, leading to a first-time SEP3 success of 74% of patients.

Lilly believed equating 87% success in SEP2 from the challenge phase of this study to 9 out of 10 men achieving successful sexual intercourse with their first vardenafil tablet was an inaccurate and misleading interpretation.

Further, the one week challenge phase of this study was conducted as an open label study; however this was not mentioned in the advertisement nor the leavepiece as an important and clinically relevant study limitation or bias.

Lilly therefore alleged that the advertisement and the leavepiece were in breach of Clauses 7.2 and 7.4 of the Code.

RESPONSE

Bayer Schering stated whilst the percentages quoted by Lilly were correct, the conclusions drawn were incorrect. Bayer Schering had never claimed that SEP2 (penetration) success equated to successful intercourse which was assessed by SEP3 (maintenance). Therefore any suggestion that Bayer Schering had made this claim (ie that SEP2 penetration equated to full successful intercourse) was based on an incorrect interpretation. All Bayer Schering's materials with this claim specifically stated that SEP2 was the measure referred to.

Bayer Schering noted that Lilly was further concerned that the one week challenge phase of Valiquette *et al* was conducted as an open label study, but that this was not mentioned in the advertisement nor the leavepiece as an important and clinically relevant study limitation or bias. Bayer Schering submitted that the open label challenge phase was neither a limitation nor a source of bias but rather a critical part of the study which was designed to examine the extent to which efficacy was sustained over a 12 week treatment period. In order to do this it was necessary to identify responders to treatment with vardenafil and exclude placebo responders. Furthermore the study was fixed at the initial vardenafil starting dose and was not a flexible dose design. Flexible dose studies of vardenafil were invariably associated with higher efficacy rates. After the open label challenge phase vardenafil responders were randomised to either placebo or vardenafil. At this point it was important that the study was double-blind in order to exclude any potential bias of assessment. In an attempt to resolve this point of dispute Bayer Schering offered to add 'Data from challenge phase of open label study' which would add further clarity to this claim. Bayer Schering had instigated this already for all future materials.

PANEL RULING

The Panel noted that during the open-label challenge phase of Valiquette *et al* 520/600 patients given a single dose of Levitra 10mg achieved SEP2 success ie penetration. Although in both the advertisement and the leavepiece a footnote to the claim noted that success was measured as achievement of SEP2, there was no mention that this meant penetration and in any event it was a principle under the Code that claims should not be qualified by the use of footnotes and the like. The Panel considered the impression given by the claim 'Works first time in 9 out of 10 men' was that for 90% of men, their first dose of Levitra resulted in successful intercourse (SEP3) and not just successful penetration (SEP2). This impression was endorsed by the claim 'Get it right first time' in the leavepiece and the strapline 'Right first time' in the advertisement. Further, the data 520/600 did not equate to 9 out of 10. The Panel ruled that the claim was misleading and had not been substantiated in breach of Clauses 7.2 and 7.4.

2 'Levitra lets them wine and dine'

This claim appeared in the leavepiece and was referenced to the Levitra summary of product characteristics (SPC).

COMPLAINT

Lilly considered that the claim was inconsistent with the SPC which stated 'The onset of activity may be delayed if taken with a high fat meal'. Lilly alleged that the claim was misleading in breach of Clause 7.2.

RESPONSE

Bayer Schering did not accept that the claim was inconsistent with the SPC. Section 4.2 of the SPC, Posology and method of administration, stated that Levitra could be taken with or without food.

The changes in pharmaocokinetics of vardenafil when taken with a high fat meal gave rise to the statement in the posology section 'The onset of activity may be delayed if taken with a high fat meal'. Section 5.2 expanded on this: 'When vardenafil is taken with a high fat meal (containing 57% fat), the rate of absorption is reduced, with an increase in the median tmax of 1 hour and a mean reduction in Cmax of 20%. Vardenafil AUC is not affected. After a meal containing 30% fat, the rate and extent of absorption of vardenafil (tmax, Cmax and AUC) are unchanged compared to administration under fasting conditions'.

The Levitra SPC stated that there were no effects on vardenafil's absorption when taken with a meal containing 30% fat. This was the fat content of a typical evening meal.

The relatively low absolute bioavailability of vardenafil and metabolism predominantly via CYP3A4 isoenzymes led to high inter- and intra-individual

variability. The inter-individual variability for Cmax and AUC was 38-59% and 37-51% respectively. The intra-individual (within subject) variability for Cmax and AUC was approximately 20% and 31% respectively. The median (range) tmax hr following a high fat meal (57% fat) was 2.0 (0.5-4.0) and after a typical evening meal (30% fat) 1.0 (0.5-4.0). These changes in primary pharmacokinetics were not considered clinically significant and indicated that exposure to vardenafil was not affected by the consumption of meals that contained high or moderate amounts of fat. Hence the SPC statement that vardenafil could be taken with and without food.

With regard to the effect of alcohol on Levitra, section 4.5 of the SPC stated that 'When vardenafil (20mg) and alcohol (mean maximum blood alcohol level of 73mg/dl) were taken together, vardenafil did not potentiate the effects of alcohol on blood pressure and heart rate and the pharmacokinetics of vardenafil were not altered'.

PANEL RULING

The Panel noted that the Levitra SPC stated that Levitra could be taken with or without food and that the onset of activity might be delayed with a high fat meal.

The Panel noted that Levitra 20mg did not potentiate the effects of alcohol (mean blood level of 73mg/dl) on blood pressure and heart rate and the pharmacokinetics of Levitra were not altered. The Panel noted that in this regard the blood alcohol limit for driving was 80mg per 100mls.

The Panel considered that given the content of the SPC insufficient information had been given in the leavepiece about the effect of food and drink. In that regard the claim 'Levitra lets them wine and dine' was misleading and a breach of Clause 7.2 was ruled.

3 'Given a choice of PDE5 inhibitors, Levitra is the one many men prefer'

This claim appeared in the leavepiece and was referenced to an abstract presented by Sommer *et al* at a North American congress in 2005.

COMPLAINT

Lilly believed that the Sommer *et al* abstract had not been peer reviewed and noted that the limitations of the study were not stated in the leavepiece; hence the claim of preference was misleading and unfair. Lilly noted that in Case AUTH/1638/10/04 Bayer had been ruled in breach of Clauses 7.2 and 7.3 for using this preference claim from this same study, in a poster at the BAUS meeting of 2004. Lilly believed the use of this claim again was a breach of Clauses 2, 7.2 and 7.3.

RESPONSE

With regard to Case AUTH/1638/10/04 Bayer Schering submitted that the ruling of a breach of the Code was in relation to the promotional use of Sommer *et al* poster (ie without prescribing information) and not the data per se. It was important to understand the data on that earlier poster were the interim results.

The data used in Bayer Schering's current promotional pieces were now final data, presented as an abstract at the North American Congress of the Ageing Male 2005. Abstracts (with the author(s) anonymised) would have been peer reviewed before acceptance at a congress. Mulhall and Montorsi (2005) reviewed preference trials and demonstrated that Sommer *et al*, unlike some others, had many of the attributes of a well designed preference trial.

PANEL RULING

The Panel noted that the Sommer abstract provided little information about the design and analysis of the study which compared preferences for vardenafil, sildenafil and tadalafil (Lilly's product Cialis) at maximum and half maximum doses. Levitra had been the preferred treatment at maximum and half maximum doses. At maximum dose 39% of patients preferred Levitra with 22% preferring sildenafil and 38% preferring tadalafil. The corresponding figures at half maximum doses were 44%, 37% and 19%.

The Panel noted Bayer Schering's submission regarding the basis of the Appeal Board's rulings in Case AUTH/1638/10/04. Although in that case the promotional use of the Sommer poster had been ruled in breach of the Code because of a lack of prescribing information, it had also been ruled in breach of the Code for the data per se. The Appeal Board had considered that the poster was misleading because it did not clearly state the length of the study period and nor did it make it sufficiently clear that only interim results were presented, the study, at that time, was still ongoing.

Turning to the case now before it, the Panel noted that the study had been completed. The Panel noted the difference in preference expressed for the products. It did not appear that there had been any statistical evaluation of the results. The Panel queried whether a difference of 39% of patients preferring vardenafil compared with 38% preferring tadalafil at maximum approved doses represented a true difference between the two products particularly in the absence of any statistically significant difference. The Panel considered that, based upon the results of Sommer *et al* (2005), the claim was misleading and unfair and breaches of Clauses 7.2 and 7.3 were ruled.

The Panel did not consider the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of censure and reserved for such use.

Complaint received	**9 July 2007**
Case completed	**17 August 2007**