ACTELION v GLAXOSMITHKLINE

Promotion of Volibris

Actelion UK and Ireland complained about two leavepieces for Volibris (ambrisentan) issued by GlaxoSmithKline UK.

A four page leavepiece headed 'Endothelin Receptor Antagonists – Drug Drug Interactions' featured a table on page 2 which listed a number of medicines down the side of the page and set out whether they could be used with bosentan (Tracleer), macitentan (Opsumit) and Volibris. These three medicines were listed across the top of the page and next to each was a reference to that medicine's summary of product characteristics (SPC). Various intersecting boxes in the table were coloured red, amber, green or grey. The grey boxes denoted that the drug drug interaction was 'Unknown' and the green boxes denoted 'No clinically relevant effect'.

Actelion noted to the requirement that when material referred to published studies, clear references must be given. The leavepiece appeared to quote the Volibris SPC as the reference for most of the information on interactions. However, Actelion could find no reference in the SPC to interactions with clarithromycin, tacrolimus and ritonavir and alleged that this information was thus unsubstantiated.

The detailed response from GlaxoSmithKline is given below.

The Panel noted that material had to be capable of substantiation and that substantiation to be provided on request. In addition references were required in certain circumstances including when promotional material referred to published studies.

The Panel noted GlaxoSmithKline's submission that the substantiation for the information regarding interactions with clarithromycin, tacrolimus and ritonavir were a number of studies and not the Volibris SPC. The Panel did not consider that the table at issue referred to a published study as such. The material provided to substantiate certain information was a number of studies but given the context there was no need to reference these studies in the leavepiece itself. Thus the Panel ruled no breach of the Code.

Actelion alleged that the leavepiece did not contain sufficient information to allow readers to make their own opinion as to the therapeutic value of the medicine. In inter-company correspondence Actelion referred to the fact that the leavepiece only provided information on drug interactions.

The Panel noted that as the leavepiece was headed 'Endothelin Receptor Antagonists – Drug Drug Interactions' readers would expect information about drug drug interactions. Health professionals would have to use other sources for information about the efficacy of the medicines listed. In the circumstances the Panel considered that only referring to interactions in the leavepiece did not mean that the leavepiece was not sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine as alleged. No breach was ruled.

The second piece was an A5 leavepiece headed 'Stockley's Drug Interactions Chart'. Stockley's corporate brand colours were used in the leavepiece which unfolded to an A3 sheet one side of which, in the form of a chart, was an 'at-a-glance' guide to common interactions between medicines frequency used in pulmonary arterial hypertension. A section to the right hand side of the chart advertised Stockley's Drug Interaction book. Beneath this was the GlaxoSmithKline corporate logo and a statement 'This interaction chart is produced through an educational grant from GlaxoSmithKline and is provided as an educational guide for health care professionals. The content of this material has been produced independently by the editorial team of Stockley's Drug Interactions'.

Actelion was concerned that the leavepiece was ambiguous in its purpose ie was it a promotional or educational item? Actelion noted that the sponsorship statement indicated the leavepiece was provided as an educational guide for health professionals. However, the reverse of the leavepiece included prescribing information for Volibris; this was not in line with PMCPA guidance that medical and educational goods and services must not bear the name of any medicine.

The Panel considered that the leavepiece was a piece of promotional material for Volibris which included the interaction chart. In effect the leavepiece also included several advertisements for Stockley's publications. The Panel considered that the description of GlaxoSmithKline's involvement could have been better worded but there was no prohibition under the Code to providing education as part of a promotional item. Indeed promotion should be informative and educational. The leavepiece was not a medical or educational good or service as meant by the Code and no breach was ruled.

Actelion UK and Ireland Limited submitted a complaint about two pieces of promotional material for Volibris (ambrisentan) issued by GlaxoSmithKline UK Limited. Volibris was indicated for the treatment of patients with pulmonary arterial hypertension (PAH) classified as WHO (World Health Organisation) Functional Class II and III, to improve exercise capacity. The materials at issue were two charts; one chart compared the drug interactions observed with bosentan, macitentan (Actelion's

products Tracleer and Opsumit respectively) and Volibris (ref UK/ABT/0023/14) and the other, using data from a standard textbook, compared the interactions between medicines frequently used in PAH, and included ambrisentan and bosentan (ref UK/ABT/0059/13). The intended audience for each leavepiece was clinicians experienced in PAH working in one of the seven UK adult PAH reference centres and prescribing target oral therapy for PAH.

This case was considered under the 2014 Code using the 2015 Constitution and Procedure.

A Interaction Chart (ref UK/ABT/0023/14)

This four page leavepiece was used between 3 September 2014 and 28 February 2015 and was headed 'Endothelin Receptor Antagonists – Drug Drug Interactions'. Page 2 featured a table which listed a number of medicines down the side of the page and set out whether they could be used with bosentan (Tracleer), macitentan (Opsumit) and Volibris. These three medicines were listed across the top of the page and next to each was a reference to that medicine's summary of product characteristics (SPC). Various intersecting boxes in the table were coloured red, amber, green or grey. Each box included text. Grey boxes denoted that the drug drug interaction was 'Unknown' and green boxes denoted 'No clinically relevant effect'. Page 3 was headed 'safety information' and referred to adverse reactions associated with Volibris. Prescribing information for Volibris was included on the outside back page.

1 Interactions with clarithromycin, tacrolimus and ritonavir

COMPLAINT

Actelion noted that Clause 7.6 stated that when material referred to published studies, clear references must be given. In that regard, Actelion noted that the leavepiece appeared to quote the Volibris SPC as the reference for all information on interactions except for those with mycophenolate mofetil and omeprazole. However, Actelion stated that it could find no reference in the Volibris SPC to interactions with clarithromycin, tacrolimus and ritonavir and alleged that this information was thus unsubstantiated.

RESPONSE

GlaxoSmithKline noted that the Code required all claims to be capable of substantiation and that substantiation be provided promptly when requested. References were only mandatory when referring to published studies including the use of quotations, tables, graphs and artwork. GlaxoSmithKline submitted that if Actelion had asked for the information relating to clarithromycin, tacrolimus and ritonavir to be substantiated during inter-company dialogue, it would have supplied Markert *et al* (2013), Mandagere *et al* (2010a) and Gillies *et al* (2011), just as it did for mycophenolate mofetil (Mandagere *et al*, 2010b) and omeprazole (Harrison *et al*, 2009).

PANEL RULING

The Panel noted that material had to be capable of substantiation and that substantiation be provided on request (Clauses 7.4 and 7.5). In addition references were required in certain circumstances including when promotional material referred to published studies.

The Panel noted GlaxoSmithKline's submission that the substantiation for the information regarding clarithromycin, tacrolimus and ritonavir were a number of studies and not the SPC. The Panel did not consider that the table on page 2 referred to a published study as such and thus Clause 7.6 did not apply. The material provided to substantiate certain information was a number of studies but given the context there was no need under Clause 7.6 to reference these studies in the leavepiece itself. Thus the Panel ruled no breach of Clause 7.6.

The Panel considered that the impression given by the reference in the leavepiece to the Volibris SPC was that all the interactions were in that SPC and this was not so. The Panel queried whether the material met the requirements of Clause 7.2 in this regard and requested that this be drawn to GlaxoSmithKline's attention.

2 Material not sufficiently complete

COMPLAINT

Actelion alleged that the leavepiece did not contain sufficient information to allow readers to make their own opinion as to the therapeutic value of the medicine. In inter-company correspondence Actelion referred to the fact that the leavepiece only provided information on drug interactions. A breach of Clause 7.2 was alleged.

RESPONSE

GlaxoSmithKline submitted that the leavepiece was intended to cover the known drug-drug interactions of bosentan, macitentan and Volibris and was not a complete review of the safety or efficacy of the medicines. A succinct safety statement was included in the leavepiece to highlight specific safety issues and provide balance.

PANEL RULING

The Panel noted the heading on page 1 of the leavepiece 'Endothelin Receptor Antagonists – Drug Drug Interactions' and considered that readers would expect information about drug drug interactions. Page 3 of the leavepiece included safety information about Volibris. The table on page 2 included a number of red boxes which were labelled variously including 'avoid macitentan', 'concomitant use not advisable' and 'contraindicated'.

In the Panel's view the leavepiece was designed to provide information about interactions. Health professionals would have to use other sources for information about the efficacy of the medicines listed in the table on page 2. The Panel noted

that Actelion had not provided information about what was missing from the chart in question. In the circumstances the Panel considered that only referring to interactions in the leavepiece did not mean that the leavepiece was not sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine as alleged. No breach of Clause 7.2 was ruled.

B Stockley's Drug Interaction Chart (ref UK/PAH/0031/13)

The A5 leavepiece was headed 'Stockley's Drug Interactions Chart'. Stockley's corporate brand colours were used in the leavepiece which unfolded to an A3 sheet one side of which, in the form of a chart, was an 'at-a-glance' guide to over 350 common interactions between medicines frequently used in PAH. A section to the right hand side of the chart advertised Stockley's Drug Interaction book. Beneath this was the GlaxoSmithKline corporate logo and a statement 'This interaction chart is produced through an educational grant from GlaxoSmithKline and is provided as an educational guide for health care professionals. The content of this material has been produced independently by the editorial team of Stockley's Drug Interactions'. Three of the four quarters on the reverse of the A3 page included advertising for Stockley's publications. The fourth quarter included the prescribing information for Volibris, information about reporting adverse events and the GlaxoSmithKline corporate logo. The leavepiece was used between 27 March 2014 and October 2014.

COMPLAINT

Actelion alleged that the leavepiece breached Clause 18.4; the company was concerned that it was ambiguous in its purpose ie was it a promotional or educational item? Actelion noted that the sponsorship statement indicated the leavepiece was provided as an educational guide for health professionals. However, the reverse of the leavepiece included prescribing information for Volibris; this was not in line with PMCPA guidance that medical and educational goods and services must not bear the name of any medicine.

RESPONSE

GlaxoSmithKline submitted that the leavepiece was used by its field-based commercial team. It was not a medical or educational good or service as such items must not bear the brand name of any medicine. The leavepiece was promotional and in that regard it was clearly branded with Volibris and carried all the obligatory information including the prescribing information.

The leavepiece advertised the complete Tenth Edition of Stockley's Drug Interactions (a world-renowned resource). As GlaxoSmithKline had commissioned Stockley to produce a chart on PAH drug interactions, information on this funding was provided on the pages where the PAH chart was reproduced. It was described as an educational guide, which GlaxoSmithKline amended to a guide (copy not supplied) when it was superseded by UK/ABT/0023/14 'Endothelin Receptor Antagonists – Drug Drug Interactions' (the leavepiece at issue in A above). The use of the word educational on an item did not constitute it being a medical or educational good or service. GlaxoSmithKline submitted that it wanted prescribers to know that the company had commissioned the PAH interactions chart, but that it had had no input to the classification of the drug interactions noted in the table, which was assessed and created by Stockley. GlaxoSmithKline had no editorial input to the leavepiece but did review and certify the content. This had been clearly explained during inter-company dialogue:

'This leavepiece is not a medical educational goods or service. It is a piece of promotional material which carries the Volibris prescribing information and other obligatory information. It reproduces the interaction table from Stockley that GlaxoSmithKline commissioned and also gives the reader information on the textbook. GlaxoSmithKline do not provide the book or online access. Had we been giving away the actual text book Stockley, then we agree it would have fallen within the scope of a medical or educational good or service.'

GlaxoSmithKline had stated that the leavepiece was a promotional piece and not a medical or educational good or service and, therefore, it denied a breach of Clause 18.4 of the 2014 Code.

PANEL RULING

The Panel examined the leavepiece. It considered that it was a piece of promotional material for Volibris which included the interaction chart. In effect the leavepiece also included several advertisements for Stockley's publications including Stockley's Drug Interactions, Tenth Edition.

The Panel considered that the description of GlaxoSmithKline's involvement could have been better worded but there was no prohibition under the Code to providing education as part of a promotional item. Indeed promotion should be informative and educational. The leavepiece was not a medical or educational good or service as meant by Clause 18.4 of the Code. The Panel thus ruled no breach of Clause 18.4.

Complaint received **9 March 2015**

Case completed **5 June 2015**