CASE AUTH/2436/9/11

GENZYME v SHIRE

VPRIV website

Genzyme complained about claims on the VPRIV (velaglucerase alfa) website, created by Shire. Genzyme further alleged that the health professionals' part of the website was easily accessible, allowing the public to read promotional claims. Genzyme marketed Cerezyme (imiglucerase). VPRIV and Cerezyme were both enzyme replacement therapies indicated in patients with Gaucher disease.

The detailed response from Shire is given below.

To the right of a table of data comparing the efficacy of Cerezyme and VPRIV was a claim that VPRIV was 'at least as effective as' Cerezyme. Genzyme submitted that 'at least as effective as' did not properly describe the results of a non-inferiority study and alleged that the claim was unbalanced, misleading and exaggerated.

The Panel noted that the data from the non-inferiority study (reported in the summary of product characteristics (SPC)) showed that the efficacy of VPRIV, measured by the increase in haemoglobin concentration, was clinically and statistically non-inferior to imiglucerase. The SPC also noted no statistically significant differences between the two medicines in terms of platelet counts and liver and spleen volumes.

The Panel noted that non-inferiority studies showed that even if one product was worse than the other it was only worse within clinically unimportant limits. The phrase 'at least as effective as' not only implied equivalence but also possible superiority, which was misleading and did not reflect the available evidence. Breaches of the Code were ruled.

With regard to the manufacture of VPRIV, Genzyme alleged that a claim that the process did not require gene manipulation was incorrect because Shire's technology introduced a gene activator sequence adjacent to a gene which was clearly gene manipulation.

The Panel noted that the claim was on the health professionals' part of the website. In the Panel's view, the manufacturing process of enzymes such as VPRIV was complicated and some health professionals would not have a deep understanding of the technical issues involved. VPRIV was produced by gene activation technology in a human cell line.

The claim at issue stated that the manufacture of VPRIV 'does not require gene manipulation' and in that regard the Panel noted that to some readers 'manipulation' would mean to manage, influence or in some other way change. In the Panel's view activating a gene would influence or change it in some way. The Panel considered that the claim was misleading and a breach of the Code was ruled.

Genzyme alleged that the claim that Shire's human genetic therapies, were 'free of animal components, thus minimising the risk of viral contamination' was irrelevant to Shire's immortalised human malignant cells and did not apply to human viruses which were most relevant to a human medicine. It was therefore incomplete, unbalanced and inaccurate.

The Panel noted that according to Shire, in 2009 the availability of Genzyme's product had been significantly adversely affected by a viral contamination; there were still some ongoing supply issues. The Panel further noted that in inter-company dialogue Shire stated that it had not claimed that the use of human cell lines minimised viral contaminants. It was the fact that no animal component was introduced into the bioreactor that minimised the risk of viral contamination, not that the cell line was a human cell line. Genzyme in response noted that Shire's argument applied to animal viruses but not human viruses and that the use of a human cell line might not reduce the risk of contamination with a human virus. The Panel considered that the claim implied that, in Shire's human genetic therapies, there was a minimal risk of contamination with any virus, animal or human. This was not so. Not introducing animal components in to the manufacturing process had no impact on the risk of contamination with human viruses. The claim was misleading and a breach of the Code was ruled.

Genzyme alleged that the health professionals' part of the website was easily accessible by members of the public in breach of the Code. Whilst patients should have access to information about their disease and treatment, the website allowed easy access to all promotional claims, including those which Genzyme considered to be disparaging, inaccurate and unsubstantiated.

The Panel noted that the Code stated that unless access to promotional material about prescription only medicines was limited to health professionals and appropriate administrative staff, a pharmaceutical company website or a company sponsored website must provide information for the public as well as promotion to health professionals with the sections for each

target audience clearly separated and the intended audience identified.

The welcome page of the VPRIV website asked the reader to enter the section of the site that was most relevant to them, by clicking on either 'I am a patient, carer or family member' or 'I am a healthcare professional'. If the reader clicked on the latter, they were asked to reconfirm that they were a health professional. Only by reconfirming their professional status could they access promotional material for VPRIV.

The Panel considered that the section providing promotional information to health professionals was clearly separated from the section containing information for the public, patient, carer or family member, and the intended audience for each section was clear. The Panel did not consider that the promotional material was intended for members of the public. The promotional material on the website in the health professional section did not constitute an advertisement to the public, nor did it encourage a member of the public to ask their health professional to prescribe a prescription only medicine. No breaches of the Code were ruled.

Genzyme Therapeutics Ltd complained about Shire Pharmaceuticals Ltd's promotion of VPRIV (velaglucerase alfa) on the website www.vpriv.co.uk. VPRIV was indicated for long-term enzyme replacement therapy (ERT) in patients with type 1 Gaucher disease. Cerezyme (imiglucerase) (marketed by Genzyme) was indicated for long-term ERT in patients with a confirmed diagnosis of non-neuronopathic (type 1) or chronic neuronopathic (type 3) Gaucher disease who exhibited clinically significant non-neurological manifestations of the disease.

Shire explained that Gaucher disease was an orphan disease (<5 patients per 10,000 population) and there were approximately 240 patients in the UK currently treated with ERT. Access to accurate information was therefore especially vital for patients, patient organisations and general health professionals as well as the specialists in the eight nationally commissioned centres that prescribed for this condition.

Shire stated that for many years Cerezyme had been the only licensed ERT for Gaucher disease. VPRIV had been in clinical development since 2004 and received EU marketing authorization in 2010. The two enzymes were similar but there were some key differences, in particular in the manufacturing process. In 2009 a viral contamination significantly affected worldwide availability of Cerezyme and the resulting challenges to the supply of this product continued to date. In response to this shortage, Shire increased the production of VPRIV and in 2009/10 made it available through an early access programme in many countries including the UK. The planned product launch was also brought forward significantly to ensure that patients who were not able to obtain Cerezyme at the time could continue ERT.

Shire did not consider that the website contained any inaccurate or unsubstantiated claims. However, in an effort to resolve the dispute amicably it had agreed to make changes, but, due to its internal review process, had been unable to agree a timeline with Genzyme. Shire had considered that some of Genzyme's requests for amending the website were unrealistic.

1 Claim 'at least as effective as'

One of the pages of the website featured a table comparing the mean change (increase) in haemoglobin concentration at nine months for imiglucerase vs VPRIV. A bullet point to the right of the table stated that VPRIV was at least as effective as the same dose of imiglucerase.

COMPLAINT

Genzyme submitted that 'at least as effective as' did not properly describe the results of a non-inferiority study which should be 'at least X% effective as' where X% was the calculated lower confidence interval of relative efficacy. Genzyme alleged that the claim was unbalanced, misleading and exaggerated the probable comparative efficacy of VPRIV in breach of Clauses 7.2 and 7.3 of the Code.

RESPONSE

Shire submitted that it was surprised to receive a complaint on this point in light of the data on the website. The table adjacent to the claim at issue contained important, relevant and robust summary statistics, presented for both intention to treat and per protocol populations, that were accurate, fair and objective. Shire stated that the data clearly demonstrated that to a high degree of certainty, VPRIV was at least as good as Cerezyme in the primary end point measure of increasing haemoglobin.

Shire stated that it had designed its non-inferiority study (study 039) with a one-sided 0.025 alpha level, which it submitted was a more conservative approach than the more widely used one-sided 0.05 level typically applied in this setting and further supported the robustness of its conclusion.

Shire stated that including all the statistical information as above, it believed the comparison was valid and in line with Clause 7.3. To support the data from the 039 study, Shire had also included on the same page the top-line results from the 025, 032 and 034 studies, which it submitted supported the efficacy of VPRIV shown in the development programme that included a phase I/II, dose finding and switch study. Copies of these studies were provided.

Shire therefore submitted that the complaint was unfounded. However, in the interests of clarity and to avoid any further difference of opinion, it had prepared a change to the statement.

PANEL RULING

The Panel noted that the claim at issue was referenced to the summary of product characteristics (SPC) for VPRIV. Section 5.1 of the SPC, Pharmacodynamic properties, gave details of, *inter alia*, study 039 which was a nine month randomized, double blinded, non-inferiority, active-comparator (imiglucerase) controlled, parallel-group efficacy study in 34 patients aged 2 years and older who were naïve to ERT. The increase in haemoglobin concentration seen with VPRIV was demonstrated to be clinically and statistically non-inferior to imiglucerase. The SPC also stated that there were no statistically significant differences between VPRIV and imiglucerase in changes in platelet counts and liver and spleen volumes after nine months of VPRIV treatment and in the time to first haemoglobin response (defined as 1g/dl increase from baseline).

The Panel noted that non-inferiority studies showed that even if one product was worse than the other it was only worse within clinically unimportant limits. The phrase 'at least as effective as' not only implied equivalence but also possible superiority, which was misleading. A breach of Clause 7.2 was ruled. The claim did not reflect the available evidence and a breach of Clause 7.3 was ruled.

2 Claim 'does not require gene manipulation'

On a page of the website headed 'About VPRIV' and under a subheading of 'Our manufacturing process' it was stated 'This technology minimizes the introduction of cloning mutations into the gene and does not require gene manipulation, unlike cell lines derived from animals or plants'.

COMPLAINT

Genzyme stated that Shire's technology introduced a gene activator sequence adjacent to a gene which was clearly 'gene manipulation'. Genzyme alleged that the claim was clearly incorrect in breach of Clause 7.2. In addition, the claim disparaged Cerezyme by implication.

RESPONSE

Shire noted that Genzyme accepted that a promoter was not part of the gene, and stated, correctly, that the technique for making VPRIV included placing a gene activator adjacent to the gene.

Shire submitted that there was a clear distinction between the definitions for genome and gene. The Oxford Dictionaries defined gene as the distinct sequence of nucleotides which formed part of a chromosome the order of which determined the order of monomers in a polypeptide, and genome as the complete set of genes or genetic material in a cell or organism. Shire submitted that the promoter sequence was not considered to be part of the gene, but might be a considerable distance away from it. Shire stated that this was absolutely not manipulation of the gene.

Shire stated it was important for readers of the website to be aware of the differences of using a naturally occurring human DNA sequence that coded for the B-glucocerebrosidase (GCR) enzyme, within a human cell expression system (as was the case for VPRIV) and given the spotlight on manufacturing, it considered it was important to be able to differentiate from the manufacturing techniques by which alternative products were made. Shire stated that the patent for Cerezyme clearly described a different method for making a version of GCR which resulted in Cerezyme having one amino acid difference to human GCR.

Shire stated using the gene activation system to make GCR did not require alteration of the nucleotide sequence of the gene and hence it stood by the claim that the production of VPRIV did not require gene manipulation. Additionally, Shire noted that the information on the text on the website did not infer any benefit, but merely stated the difference of its process. Genzyme's claim that there were disparaging implications for its process was incorrect and therefore this was an unfounded allegation.

PANEL RULING

The Panel noted that the claim at issue was on that part of the website intended for health professionals. In the Panel's view, the manufacturing process of enzymes such as VPRIV and Cerezyme were complicated and some health professionals would not have a deep understanding of the technical issues involved. The VPRIV SPC stated that velaglucerase alfa was produced by gene activation technology in a human cell line.

The claim at issue stated that the manufacture of VPRIV 'does not require gene manipulation' and in that regard the Panel noted that to some readers 'manipulation' would mean to manage, influence or in some other way change. In the Panel's view activating a gene would influence or change it in some way. The Panel considered that the claim was misleading and a breach of Clause 7.2 was ruled.

The Panel noted that although Genzyme had also alleged that the claim disparaged Cerezyme by implication, it had not cited Clause 8.1. Paragraph 5.3 of the Constitution and Procedure required companies to state those clauses which are alleged to have been breached. With no allegation of a breach of Clause 8.1, the Panel could not make a ruling on this point.

3 Claim 'Shire HGT's [human genetic therapies] bioreactor cell lines are free of animal components, thus minimising the risk of viral contamination…'

This claim appeared on a page of the website

headed 'About VPRIV' and under a subheading of 'Minimising manufacturing risk'.

COMPLAINT

Genzyme alleged that the claim was somewhat irrelevant to Shire's immortalised human malignant cells and obviously did not apply to human viruses which were most relevant to a human medicine. It was therefore incomplete, unbalanced and inaccurate, and in breach of Clause 7.2. Genzyme also alleged that the claim disparaged its manufacturing methods for Cerezyme by implication.

RESPONSE

Shire was unclear as to why Genzyme had complained about the factual statements Shire made about its own manufacturing process, nor how Genzyme considered the statements referred to its product as, in this text, Shire did not reference any process other than its own and it did not have any depth of knowledge of the manufacturing processes used by Genzyme.

Shire submitted that in order to address questions in the market about whether it could be at risk of viral infection, it had presented basic facts about its manufacturing processes. Shire submitted this was an unfounded allegation.

PANEL RULING

The Panel noted that according to Shire, in 2009 the availability of Genzyme's product had been significantly adversely affected by a viral contamination; there were still some ongoing supply issues. The Panel further noted that in inter-company dialogue Shire stated that it had not claimed that the use of human cell lines minimised viral contaminants. It was the fact that no animal component was introduced into the bioreactor that minimised the risk of viral contamination, not that the cell line was a human cell line. Genzyme in response noted that Shire's argument applied to animal viruses but not human viruses and that the use of a human cell line might not reduce the risk of contamination with a human virus. The Panel considered that the claim implied that, in Shire's human genetic therapies, there was a minimal risk of contamination with any virus, animal or human. This was not so. Not introducing animal components in to the manufacturing process had no impact on the risk of contamination with human viruses. The claim was misleading and a breach of Clause 7.2 was ruled.

The Panel noted that although Genzyme had also alleged that the claim disparaged Cerezyme by implication, it had not cited Clause 8.1. Paragraph 5.3 of the Constitution and Procedure required companies to state those clauses which are alleged to have been breached. With no allegation of a breach of Clause 8.1, the Panel could not make a ruling on this point.

4 Alleged promotion to the public

COMPLAINT

Genzyme noted that the portion of the website purportedly allocated for the use of health professionals was easily accessible by members of the public in breach of Clauses 22.1, 22.2, 24.1 and 24.3. Whilst Genzyme strongly believed that patients should have access to reliable, balanced and clear information about their disease and treatment, the configuration of the website allowed easy access to all promotional claims, including those which Genzyme considered to be disparaging, inaccurate and unsubstantiated.

RESPONSE

Shire submitted that it was particularly dismayed by this complaint and considered that Genzyme was time wasting to take Shire away from its focus of providing effective medicines to patients. Shire stated that the website clearly met the guidance on the use of the Internet as set out in Clause 24.1. The claims at issue above were in the health professional section of the website which Shire submitted was clearly separated from the 'Patient, carer or family member' section at the point of entry into the site. Shire denied a breach of Clause 24.3. Shire stated that the configuration of its website with clearly separated and identified points of access to either the health professional or patient sections was a widely used practice. The website met the requirements of Clause 24 and Shire denied breaches of Clauses 22.1 or 22.2.

Shire provided a copy of a leavepiece that promoted the website to health professionals. The website had never been promoted directly to the public. The patient organisation, The Gauchers Association, of its own volition, had placed a news story about the site on its own website www.gaucher.org.uk/news.php (a screen shot of the relevant section of the patient organisation's website was provided). Shire engaged with The Gaucher Association to review the patient section of the VPRIV website for comments or feedback before launch. Shire submitted that The Gaucher Association pro-actively publicised any information that it considered could be of value to its members.

PANEL RULING

The Panel noted that the supplementary information to Clause 24.1 stated that unless access to promotional material about prescription only medicines was limited to health professionals and appropriate administrative staff, a pharmaceutical company website or a company sponsored website must provide information for the public as well as promotion to health professionals with the sections for each target audience clearly separated and the intended audience identified.

The Panel noted that the welcome page of the VPRIV website asked the reader to enter the section

of the site that was most relevant to them. The options were to click on either 'I am a patient, carer or family member' or 'I am a healthcare professional'. If the reader clicked on the latter, they were taken to a page that stated that information was intended for health professionals only and asked to tick a box to confirm that they were a health professional. If the box was ticked, the reader could access promotional material for VPRIV by clicking a 'Continue' button. If the box was not ticked, the reader could not access promotional material when the 'Continue' button was clicked. The Panel noted that on entering the section for the patient, carer or family member, the first page stated that the website was developed to provide information to the general public, patients and their families, and also to health professionals about velaglucerase alfa.

The Panel noted that the supplementary information to Clause 24.1 referred to material for health professionals and material for the public. It did not mention material for patients that had been prescribed the medicine. The Panel noted that the website was promoted to health professionals only.

The Panel considered that the section providing promotional information to health professionals was clearly separated from the section containing information for the public, patient, carer or family member, and the intended audience for each section was clear. The Panel ruled no breach of Clause 24.1. The Panel did not consider that the promotional material was intended for members of the public and ruled no breach of Clause 24.3. The promotional material on the website in the health professional section did not constitute an advertisement to the public, nor did it encourage a member of the public to ask their health professional to prescribe a prescription only medicine. No breach of Clauses 22.1 and 22.2 was ruled.

Complaint received **22 September 2011**

Case completed **7 November 2011**