WYETH v ROCHE and CHUGAI

Press statements regarding Actemra

Wyeth complained about Roche and its media activities regarding its unlicensed medicine Actemra (tocilizumab). Actemra was being developed jointly by Roche and Chugai Pharma Europe for the treatment of rheumatoid arthritis (RA). Wyeth's product Enbrel (etanercept) was indicated for the treatment of moderate to severe active rheumatoid arthritis in adults in certain circumstances.

Inter-company dialogue had been unsuccessful and while Wyeth understood that Roche had made a voluntary admission to the Authority about a media release (Cases AUTH/2154/8/08 and AUTH/2155/8/08) it had no option but to submit a formal complaint.

The claims 'New Data Reveals Tocilizumab Is The First And Only Biologic Drug To Show Superiority Over Current Standard Of Care In Rheumatoid Arthritis' and 'No previous biologic therapy has demonstrated superiority compared to [methotrexate] MTX' appeared in a Roche media statement dated 13 June. Wyeth alleged that these claims were inaccurate, misleading and did not reflect up-to-date evidence. The press release referred to tocilizumab being the only biologic agent to show superiority to methotrexate (MTX). This was incorrect as there was a wealth of evidence supporting the superiority over MTX of other biologic agents with existing marketing authorizations (Bathon *et al*, 2000).

The detailed response of Roche and Chugai is given below.

The Panel considered that its rulings in Cases AUTH/2154/8/08 and AUTH/2155/8/08 were relevant. In Cases AUTH/2154/8/08 and AUTH/2155/8/08 the Panel considered that the heading to the media release, 'New data reveals tocilizumab is the first and only biologic drug to show superiority over current standard of care in rheumatoid arthritis' was a strong unqualified claim. The first paragraph of the media release explained that the current standard of care was methotrexate. The Panel noted the companies' submission that other biologic therapies had shown superiority but unlike tocilizumab not across all American College of Rheumatology (ACR) measures. Superiority had not been uniformly shown in this regard at 6 months and it was this point that was intended to be conveyed in the press release. The Panel was concerned about the general claims for superiority. The media release also contained the claim 'No previous biologic therapy has demonstrated superiority compared to MTX' which was not so. The Panel noted that the media release had been sent to UK national and medical media. The product was not authorized in the UK and the media release was extremely positive; it used 'novel', innovative' and 'most exciting' to describe the product. The Panel considered that the media release was not factual and that the results of the AMBITION study had not been presented in a balanced way. The media release would raise unfounded hopes of successful treatment. Thus the Panel ruled a breach of the Code.

The Panel considered that given its comments above high standards had not been maintained. A breach of the Code was ruled. Although noting its rulings, the Panel did not consider that the media release warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use.

Turning to Cases AUTH/2160/8/08 and AUTH/2161/8/08 the Panel noted that the alleged breaches of the Code in these cases differed from Cases AUTH/2154/8/08 and AUTH/2155/8/08 albeit that the allegations were similar ie that the claims were misleading. The Panel considered that the claims were misleading and could not be substantiated. Breaches of the Code were ruled.

The claim 'What made this result even more impressive was the fact that 12-18% of the study population had failed to respond to one or more prior anti-TNF [tumour necrosis factor] therapies, leaving them with little hope of further symptom relief from these traditional treatments' also appeared in a Roche media statement dated 13 June.

Wyeth alleged that the claim employed emotive, inappropriate language ('impressive') and did not objectively represent the findings. There was a wealth of evidence showing that patients benefited from sequential use of biological therapies. To claim that patients who had failed anti-TNF therapy would be left with little hope of further symptom relief from these traditional treatments was misleading in breach of the Code. Referring to anti-TNF agents as traditional treatment was inappropriate. The medical literature referred to classic disease modifying antirheumatic drugs (DMARDs) such as MTX as traditional, whilst anti-TNF agents were considered to be a relatively new class of medicines. In Wyeth's view, this reference therefore aimed to convey an advantage of tocilizumab over anti-TNF agents. This was factually wrong, unsubstantiated and disparaging.

The Panel noted the respondents' submission that

the statement relating to 'little hope of further symptom relief' was true if patients had failed on three anti-TNFs. To state that the same was true when patients had failed to respond to one or more prior anti-TNF therapies was thus misleading, unsubstantiable and exaggerated. Breaches of the Code were ruled. The Panel further considered that the statement disparaged anti-TNF therapies. A breach of the Code was ruled.

The claim 'Tocilizumab (to be called Actemra) is the first humanised interleukin-6 (IL-6) receptor inhibiting monoclonal antibody and represents a novel mechanism of action to treat RA, a disease with a high unmet medical need. This treatment is not yet licensed in Europe and is the result of research collaboration by Roche and Chugai, it is being co-developed globally' appeared on the Roche UK Website.

Wyeth noted that 'reference information' could be provided on a company website as an up-to-date resource for the public. However, reference information must relate to prescription only medicines which had a marketing authorization. As tocilizumab was not licensed, this was a breach of the Code. As there had been a clear advertisement to the public by Roche, this had also breached the Code.

Wyeth alleged that high standards had not been maintained. This was especially important as tocilizumab did not have a UK marketing authorization.

The Panel considered that a press release was different to reference information. The Panel did not consider it was necessarily unacceptable for a press release to refer to an unlicensed medicine, it would depend what was said. The Panel noted that the press release was on the Roche UK website in an area clearly marked for the media; it was not in a section which provided reference information for the public. The Panel did not consider that the press release promoted an unlicensed medicine and thus no breach of the Code was ruled. The Panel did not consider that the press release advertised tocilizumab to the public. No breach of the Code was ruled.

Given its rulings above the Panel did not consider that high standard had not been maintained. No breach of the Code was ruled.

Wyeth noted that a number of press articles in the Daily Mail, 16 June 2008, which resulted from a Roche press release, had shared the same style of promotional claims mentioned above, had been released following the European League Against Rheumatism (EULAR) meeting. Wyeth had tried unsucessfully to obtain the necessary press releases from Roche. Wyeth found this unacceptable.

With regard to the claim 'Tocilizumab is the first treatment to outperform the standard therapy methotrexate, when used in isolation', Wyeth alleged that etanercept monotherapy had shown superior efficacy in relation to MTX in clinical trials, and the summary of product characteristics (SPC) reflected this. Wyeth alleged that the claim was factually incorrect, did not reflect the up-to-date evaluation of all current evidence, could not be substantiated and raised unfounded hopes of successful treatment.

The Panel considered that its consideration of this point was covered by its rulings above. Breaches of the Code were ruled.

Wyeth alleged that a price had not been established for tocilizumab, and therefore the claim '… expensive anti-TNF drugs' was misleading as it implied that tocilizumab had a price advantage. This raised unfounded hopes of successful treatment.

The Panel noted that the press release of 13 June 2008 had not referred to the cost of anti-TNF therapies thus no breach was ruled.

With regard to the claim '[Anti-TNFs] can be effective for a while, but eventually patients build up resistance to them' Wyeth alleged that etanercept had not been shown to induce neutralising antibodies in humans, and there was a wealth of evidence to suggest that patients did not develop resistance against Enbrel therapy. The claim was factually incorrect, disparaging and raised unfounded hopes of successful treatment.

The Panel noted that the press release of 13 June 2008 had not referred to the development of resistance to anti-TNF therapies thus no breach of the Code was ruled.

Wyeth alleged that taking into account the above breaches of the Code, Roche had brought discredit upon and reduced confidence in the industry, in breach of Clause 2.

Although noting its rulings above, the Panel did not consider that these cases warranted a ruling of a breach of Clause 2 of the Code which was a sign of particular censure and reserved for such.

With regard to Wyeth's request that a corrective statement be issued, the Panel noted that it could not require a corrective statement to be published. That sanction was available to the Appeal Board.

Wyeth Pharmaceuticals complained about Roche Products Ltd and its media activities regarding its unlicensed medicine Actemra (tocilizumab). Actemra was being developed jointly by Roche and Chugai Pharma Europe Ltd for the treatment of rheumatoid arthritis. Wyeth's product Enbrel (etanercept) was indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adults in certain circumstances.

Inter-company dialogue had been unsuccessful and

while Wyeth understood that Roche had made a voluntary admission to the Authority about a media release (Cases AUTH/2154/8/08 and AUTH/2155/8/08) it nonetheless considered that its complaint to Roche had not been resolved and so it had no option but to submit a formal complaint.

This case was considered under the 2006 Code using the 2008 Constitution and Procedure.

COMPLAINT

A Medical News Today

The claims at issue in points 1 and 2 below appeared in a Roche media statement dated 13 June.

1 Claims 'New Data Reveals Tocilizumab Is The First And Only Biologic Drug To Show Superiority Over Current Standard Of Care In Rheumatoid Arthritis' and 'No previous biologic therapy has demonstrated superiority compared to MTX'

COMPLAINT

Wyeth alleged that these claims were in breach of Clauses 7.2, 7.3 and 7.4 as they were inaccurate, misleading and did not reflect up-to-date evidence. The press release referred to tocilizumab being the only biologic agent to show superiority to methotrexate (MTX). This was incorrect as there was a wealth of evidence supporting the superiority over MTX of other biologic agents with existing marketing authorizations (Bathon *et al*, 2000).

RESPONSE

Roche and Chugai provided a joint response and submitted that tocilizumab was the first anti-interleukin 6 (IL-6) receptor monoclonal antibody to be developed for the management of rheumatoid arthritis. It was the first product to be born from the Chugai and Roche development collaboration. The results from the tocilizumab development programme were not only of significance and relevance medically but also from a financial services perspective. The media release was therefore deemed newsworthy.

The media statement covered the release of two data sets presented at the European League Against Rheumatism (EULAR) meeting in Paris. The main body of the release covered the presentation of data from the AMBITION study (Tocilizum**a**b versus **M**ethotrexate Double-**B**lind **I**nvestigative **T**rial **I**n M**on**otherapy) (Jones *et al* 2008) and also referred to the RADIATE study (**R**esearch on Tocilizum**a**b **D**etermining eff**i**cacy after **A**nti-**T**NF failur**e**s) (Emery *et al* 2007).

Both studies represented an important development in the management of rheumatoid arthritis. AMBITION was the first study to categorically demonstrate superiority over MTX when using the regulatory required American College of Rheumatology (ACR) scoring system of 20, 50 and 70% improvement from baseline at 6 months. No other biologic therapy had shown this. Etanercept had shown superiority at different time points with different measuring techniques (eg X ray) (Bathon *et al*, Genovese *et al* 2002) but this media release referred to signs and symptoms across the ACR 20, 50 and 70 core set at 6 months, not partial response eg ACR 70 only at 6 months. The companies fully accepted, and had never suggested otherwise, that etanercept had shown superiority when using X ray changes (not signs and symptoms) at 2 years (Genovese *et al*).

Roche and Chugai accepted that when the media release was reviewed, if the headline statements were read independently, it would not fully explain the context in which the claims were made; this was why the companies referred the matter to the Authority (Cases AUTH/2154/8/08 and AUTH/2155/8/08). Wyeth had stated that unless Roche and Chugai issued a corrective statement Wyeth would refer the matter to the Authority. In order to guarantee such a statement to be published, the companies would have had to pay for advertising space. As tocilizumab was not licensed such an advertisement would have been in breach of the Code. Roche and Chugai therefore decided that a corrective statement would not be possible under the Code and thus referred the matter to the Authority. The companies were disappointed that Wyeth had referred this matter as the two claims, 'New data reveals Tocilizumab is the first and only biologic drug to show superiority over current standard of care in RA' and 'No previous biologic therapy has demonstrated superiority compared to MTX' were being dealt with under Cases AUTH/2154/8/08 and AUTH/2155/8/08.

PANEL RULING

The Panel considered that its rulings in Cases AUTH/2154/8/08 and AUTH/2155/8/08 were relevant.

Cases AUTH/2154/8/08 and AUTH/2155/8/08

The Panel considered that the heading to the media release, 'New data reveals tocilizumab is the first and only biologic drug to show superiority over current standard of care in rheumatoid arthritis' was a strong unqualified claim. The first paragraph of the media release explained that the current standard of care was methotrexate. The Panel noted the companies' submission that other biologic therapies had shown superiority but unlike tocilizumab not across all ACR measures. Superiority had not been uniformly shown in this regard at 6 months and it was this point that was intended to be conveyed in the press release. The Panel was concerned about the general claims for superiority. The media release also contained the

claim 'No previous biologic therapy has demonstrated superiority compared to MTX' which was not so. The Panel noted that the media release had been sent to UK national and medical media. The product was not authorized in the UK and the media release was extremely positive; it used 'novel', innovative' and 'most exciting' to describe the product. The Panel considered that the media release was not factual and that the results of the AMBITION study had not been presented in a balanced way. The media release would raise unfounded hopes of successful treatment. Thus the Panel ruled a breach of Clause 20.2 of the 2006 Code.

The Panel considered that given its comments above high standards had not been maintained. A breach of Clause 9.1 was ruled.

Although noting its rulings above, the Panel did not consider that the media release warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use.

Cases AUTH/2160/8/08 and AUTH/2161/8/08

The Panel noted that the alleged breaches of the Code in these cases differed from Cases AUTH/2154/8/08 and AUTH/2155/8/08 albeit that the allegations were similar ie that the claims were misleading. The Panel considered that the claims were misleading and could not be substantiated. Breaches of Clauses 7.2, 7.3 and 7.4 were ruled.

2 Claim 'What made this result even more impressive was the fact that 12-18% of the study population had failed to respond to one or more prior anti-TNF therapies, leaving them with little hope of further symptom relief from these traditional treatments'

COMPLAINT

Wyeth alleged that the claim employed emotive, inappropriate language ('impressive') and did not objectively represent the findings in breach of Clause 7.10. There was a wealth of evidence showing that patients benefited from sequential use of biological therapies. To claim that patients who had failed anti-tumour necrosis factor (anti-TNF) therapy would be left with little hope of further symptom relief from these traditional treatments was misleading in breach of Clause 7.3. Referring to anti-TNF agents as traditional treatment was inappropriate. The medical literature referred to classic disease modifying antirheumatic drugs (DMARDs) such as MTX as traditional, whilst anti-TNF agents were considered to be a relatively new class of medicines. In Wyeth's view, this reference therefore aimed to convey an advantage of tocilizumab over anti-TNF agents. This was factually wrong, unsubstantiated and disparaging in breach of Clauses 7.2, 7.4 and 8.1.

RESPONSE

Roche and Chugai noted that the claim related to the RADIATE study. Traditionally patients with rheumatoid arthritis were initially managed with DMARDs and then by the addition of anti-TNF therapy. Anti-TNFs had been available in the UK for the last 9 years and were widely accepted as standard therapy; they had been recommended by the National Institute for Health and Clinical Excellence (NICE) as an option for the treatment of moderate to severe rheumatoid arthritis following the failure to response to a least two DMARDs. To suggest that anti-TNFs were not part of standard, traditional therapy did not reflect the long standing and wide ranging use of these therapies.

Unfortunately around a third of patients would either fail to respond, lose response or not tolerate anti-TNFs (Hyrich *et al* 2007). These patients were difficult to manage. Roche's product MabThera (rituximab) was indicated in combination with MTX for adults with severe active rheumatoid arthritis who had an inadequate response or intolerance to other DMARDs including one or more TNF inhibitor therapies. NICE recommended rituximab as an option for the management of anti-TNF inadequate responders, however, again, not all patients would respond, nor was it suitable for all patients. There was, therefore, a large unmet need.

Data from the sequential use of anti-TNFs was consistent, largely observational in nature with a population with varying baseline characteristics (van Vollenhoven 2007). Currently NICE had issued a final appraisal determination (FAD) stating that, in its opinion the sequential use of anti-TNFs would not be recommended. This was currently being appealed.

The statement relating to 'little hope of further symptom relief' was factually correct when patients had failed three anti-TNFs. In the event that patients had failed three anti-TNFs there was little hope of any symptom relief from restarting patients on these therapies. Roche and Chugai, however accepted that by not specifying three anti-TNFs within the release and instead using the term one or more anti-TNFs this might not have been as clear as it could have been.

PANEL RULING

The Panel noted the respondents' submission that the statement relating to 'little hope of further symptom relief' was true if patients had failed on three anti-TNFs. To state that the same was true when patients had failed to respond to one or more prior anti-TNF therapies was thus misleading, unsubstantiable and exaggerated. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled. The Panel further considered that the statement disparaged anti-TNF therapies. A breach of Clause 8.1 was ruled.

B Roche UK Website

1 'Tocilizumab (to be called Actemra) is the first humanised interleukin-6 (IL-6) receptor inhibiting monoclonal antibody and represents a novel mechanism of action to treat RA, a disease with a high unmet medical need. This treatment is not yet licensed in Europe and is the result of research collaboration by Roche and Chugai, it is being co-developed globally'

COMPLAINT

Wyeth noted that the Code allowed 'reference information' to be provided on a company website as an up-to-date resource for the public on that company's prescription only medicines (supplementary information to Clause 20.2). However, reference information must relate to prescription only medicines which had a marketing authorization. As tocilizumab was not licensed, this was a breach of Clause 3.1. As there had been a clear advertisement to the public by Roche, this had also breached Clause 20.1.

Wyeth alleged that high standards had not been maintained. This was especially important as tocilizumab did not have a UK marketing authorization. In view of this Clause 9.1 had also been breached.

RESPONSE

The companies noted that this statement was in the editor's notes at the end of a press release (dated 22 August 2007) that was about Roche's other rheumatoid arthritis treatment rituximab and was clearly placed within the press area of the Roche UK website. This area of Roche's corporate website was clearly labelled 'media'. To source the press statement, 'tocilizumab' had to be entered into the website search engine. Its visibility on the website was therefore extremely limited and reasonable care was taken to ensure that information was only accessed by the audience for which was intended.

PANEL RULING

The Panel noted that although Roche and Chugai had both responded to this point, the press release was only available on the Roche website. Its rulings would only apply to Roche.

The Panel noted that the supplementary information to Clause 20.2, Information to the Public, stated that the primary purpose of reference information was to be a library resource for the public giving information about prescription only medicines with marketing authorizations. Examples given in the supplementary information included summaries of product characteristics, the package information leaflet etc. The Panel considered that a press release was different to reference information. The Panel did not consider it was necessarily unacceptable for a press release to refer to an unlicensed medicine it would depend what was said. The Panel noted that the press release was on the Roche UK website in an area clearly marked for the media; it was not in a section which provided reference information for the public. The Panel did not consider that the press release promoted an unlicensed medicine and thus no breach of Clause 3.1 was ruled. The Panel did not consider that the press release advertised tocilizumab to the public. No breach of Clause 20.1 was ruled.

Given its rulings above the Panel did not consider that high standard had not been maintained. No breach of Clause 9.1 was ruled.

C Claims in the Daily Mail, 16 June 2008

Wyeth noted that the following press articles, which shared the same style of promotional claims mentioned above, had been released following the EULAR meeting. The relevant newspapers and PR companies had confirmed the source to be a Roche press release. Wyeth had tried to obtain the necessary press releases from Roche but had not been successful. Wyeth found this unacceptable.

1 Claim 'Tocilizumab is the first treatment to outperform the standard therapy methotrexate, when used in isolation'

COMPLAINT

Wyeth alleged that etanercept monotherapy had shown superior efficacy in relation to MTX in clinical trials, and the summary of product characteristics (SPC) reflected this: 'Enbrel can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate'. Wyeth alleged that the claim was factually incorrect, did not reflect the up-to-date evaluation of all current evidence and could not be substantiated in breach of Clauses 7.2 and 7.4. Wyeth further alleged that the claim raised unfounded hopes of successful treatment in breach of Clause 20.2.

RESPONSE

The companies noted that the claim 'Tocilizumab is the first treatment to outperform the standard therapy methotrexate when used in isolation' related to the claims already being considered in Cases AUTH/2154/8/08 and AUTH/2155/8/08.

PANEL RULING

The Panel considered that its consideration of this point was covered by its rulings in point A1 above. Breaches of Clauses 7.2, 7.4 and 20.2 were ruled.

2 Claim '… expensive anti-TNF drugs'

COMPLAINT

Wyeth alleged that a price had not been established for tocilizumab, and therefore it was misleading to make a comparison with anti-TNF. NICE had recommended etanercept be used in multiple indications because it was considered to be a cost-effective treatment. The claim implied that tocilizumab had a price advantage. This was misleading in breach of Clauses 7.2, 7.3, 7.4 and 8.1. Wyeth further alleged that the claim raised unfounded hopes of successful treatment in breach of Clause 20.2.

RESPONSE

Roche and Chugai submitted that this claim was the author's own; the media release did not refer to cost. The companies took no responsibility for this claim.

PANEL RULING

The Panel noted that the press release of 13 June 2008 had not referred to the cost of anti-TNF therapies thus no breach of Clauses 7.2, 7.3, 7.4, 8.1 and 20.2 were ruled.

3 Claim '[Anti-TNFs] can be effective for a while, but eventually patients build up resistance to them'

COMPLAINT

Wyeth alleged that etanercept had not been shown to induce neutralising antibodies in humans, and there was a wealth of evidence to suggest that patients did not develop resistance against Enbrel therapy. This statement was therefore factually incorrect and disparaging in breach of Clauses 7.2, 7.3, 7.4 and 8.1. Wyeth further alleged that the claim raised unfounded hopes of successful treatment in breach of Clause 20.2 of the Code.

RESPONSE

As in point C2 above, Roche and Chugai noted that this claim about developing resistance to anti-TNF therapy was the author's own. No reference to durability of response was made in the media release. The companies therefore took no responsibility for this claim.

PANEL RULING

The Panel noted that the press release of 13 June 2008 had not referred to the development of resistance to anti-TNF therapies thus no breach of Clauses 7.2, 7.3, 7.4, 8.1 and 20.2 were ruled.

4 Conclusion

COMPLAINT

Wyeth alleged that taking into account the above breaches of the Code, Roche had brought discredit upon and reduced confidence in the industry, in breach of Clause 2.

Wyeth requested corrective statements in all relevant rheumatology journals, journals relevant to UK payers and the BMJ, admitting that misleading and incorrect statements had been widely publicised. Wyeth would expect to verify all relevant corrective statements for accuracy, given the significance of the claims.

RESPONSE

Roche and Chugai did not submit a specific response to this point.

PANEL RULING

Although noting its rulings above, the Panel did not consider that these cases warranted a ruling of a breach of Clause 2 of the Code which was a sign of particular censure and reserved for such.

With regard to Wyeth's request that a corrective statement be issued, the Panel noted that it could not require a corrective statement to be published. That sanction was available to the Code of Practice Appeal Board.

Complaint received **18 August 2008**

Cases completed **29 October 2008**