REGULATORY AFFAIRS CONSULTANT v ROCHE

Articles about MabThera in the lay press

A regulatory affairs consultant and scientist/writer, complained about articles discussing the early use of MabThera (rituximab) in rheumatoid arthritis (RA) which were published in the Daily Telegraph and The Times and mentioned on television. MabThera was marketed by Roche Products.

Mabthera was indicated *inter alia*, in combination with methotrexate (MTX) for RA patients with severe active disease who had had an inadequate response or intolerance to other disease modifying anti-rheumatic drugs (DMARDs).

The complainant alleged that the reproduced Roche press release describing the wonders of off-label use of rituximab was advertising. It was unbalanced and pushed dangerous medicines to the public. There was no mention of the extremely dangerous side effects. Was this allowed? It made a joke of the medicine approval procedure.

In subsequent correspondence the complainant noted that although MabThera was indicated for rheumatoid arthritis in some cases it was indicated to be used as the articles described. The complainant alleged that the newspaper and television articles were a marketing campaign disguised as news. The article in The Times was almost a copy of a press release reporting details of a clinical trial. It made claims for the medicine, including a 30% efficacy rate, which appeared rather low. However, the article did not mention any of the serious side effects or even refer to the prescribing information.

The complainant alleged that the material was designed to get patients to campaign for doctors to give them MabThera while not making clear that it had life threatening side effects; the list of severe adverse reactions should be included to give them a balanced view.

The complainant alleged that there was clearly a conflict of interest and the lead investigator who was mentioned in the press was obviously employed by Roche.

The complainant found the blatant use of the press for medicine marketing to be cynical.

The detailed response from Roche is given below.

The Panel noted that although the complainant had complained about articles in the UK press, she had provided a copy of the global press release. The global press release had not been issued in the UK. The UK press release detailed trial results as presented at a major European conference. It was stated that 30.5% of the RA patients taking rituximab and MTX achieved remission vs 12.5% of those taking MTX alone. The Panel considered that the UK press release was written in a factual, balanced and non promotional manner; it clearly stated that rituximab was not licensed for early RA. A short paragraph also referred to side effects such as hypertension, nausea and upper respiratory tract infections. It was stated that as with all RA therapies, a small proportion of more serious side-effects were seen.

The Panel did not consider that the press release raised unfounded hopes of successful treatment or was misleading with respect to the safety of the product.

The Panel considered that any good news story about a medicine would have an inevitable positive impact but nonetheless it did not consider that statements had been made for encouraging patients to ask their health professional to prescribe rituximab. The press release was not an advertisement *per se* for rituximab and nor was it disguised promotion. The Panel noted that rituximab was not indicated for use in early RA however it did not consider that the press release promoted an unlicensed indication. In the Panel's view Roche had not failed to maintain high standards. No breaches of the Code were ruled including no breach of Clause 2.

A regulatory affairs consultant and scientist/writer, complained about articles discussing MabThera (rituximab) that appeared in the Daily Telegraph ('Drug hope for arthritis victims') and The Times ('Drug can curb joint damage at the very start of arthritis') and mentioned on television on 16 June 2009. MabThera was marketed by Roche Products Limited.

MabThera was indicated, *inter alia*, in combination with methotrexate (MTX) for rheumatoid arthritis (RA) patients with severe active disease who had had an inadequate response or intolerance to other disease modifying anti-rheumatic drugs (DMARDs).

COMPLAINT

The complainant alleged that the advertisement (well, reproduced Roche press release) describing the wonders of off-label use of rituximab, which was represented as an article, was in fact advertising. The article was unbalanced and pushed dangerous medicines to the public. There was no mention of the extremely dangerous side effects. Was this allowed? It made a joke of the medicine approval procedure.

In a subsequent response the complainant noted that she had made a mistake. MabThera was indicated for RA in some cases. However, she was not sure that it was indicated to be used as the articles described. The complainant alleged that the articles printed in The Times, The Telegraph and mentioned on television on 16 June 2009 were a marketing campaign disguised as news. The article in The Times was almost a copy of a press release reporting details of a clinical trial. It made claims for the medicine, including a 30% efficacy rate, which appeared rather low. However, the article did not mention any of the serious side effects or even refer to the prescribing information.

The complainant alleged that this article was designed to get patients to campaign for doctors to give them the medicine while not making clear that the medicine had life threatening side effects.

This made the complainant very angry to constantly see newspapers publishing obvious marketing related material.

In a subsequent response the complainant enclosed a copy of the Roche press release. The complainant alleged that there was clearly a conflict of interest and the lead investigator who was mentioned in the press was obviously employed by Roche.

However, the complainant was not sure that Roche was the problem, but it was the newspapers which printed the stuff. The newspapers were simply reproducing press releases, meant to support the share price of the pharmaceutical company, and, of course, to ensure the public made a big noise to be prescribed the medicines. The complainant found the blatant use of the press for medicine marketing to be cynical.

The actual article was unbalanced, there was no mention that the proposed treatment caused many adverse events.

The complainant alleged that the newspapers, not the pharmaceutical company, were at fault here. They had not checked out the story, but simply reproduced a press release and should be held to account for the inaccuracy of the story.

The complainant was not based in the UK and had only seen the Internet version of these articles, but assumed that the content was the same.

The complainant provided a list of severe adverse reactions, many were obviously life threatening, taken from the MabThera summary of product characteristics (SPC).

> Serious adverse reactions observed in post-marketing surveillance: *Serious viral infection. Late neutropenia, pancytopenia, aplastic anaemia. Severe events in patients with prior cardiac condition or cardiotoxic chemotherapy, heart failure, myocardial infarction. Hearing loss. Severe vision loss. Multi-organ failure. Infusion related reactions, anaphylaxis, tumour lysis syndrome, cytokine release syndrome, serum sickness. Very rare cases of Hepatitis B reactivation, including fulminant hepatitis with fatal outcome. Progression of pre-existing Kaposi's sarcoma, mainly in patients with HIV. Cranial neuropathy, peripheral neuropathy, facial nerve palsy, loss of other senses. Renal failure. Bronchospasm, respiratory failure, pulmonary infiltrates, interstitial pneumonitis. Gastro-intestinal perforation. Severe bullous skin reactions, toxic epidermal necrolysis. Vasculitis (various types)*.

The complainant alleged that if the article was aimed at the public who were unfortunate enough to suffer with arthritis, then the list of severe adverse reactions should be included to give them a balanced view.

When writing to Roche the Authority asked it to respond in relation to Clauses 2, 3.2, 9.1, 12.1, 22.1 and 22.2 of the Code.

RESPONSE

Roche noted that the articles at issue were published in The Times and The Daily Telegraph on 16 June 2009 following the presentation of data from the rituximab IMAGE trial at the European League against Rheumatism (EULAR) meeting in Denmark on 11 June 2009. Roche UK had issued a press release around the presentation of these data to the medical and consumer press on 15 June. Roche UK issued this press release to the UK media including The Times and Daily Telegraph and not the global press release as sourced by the complainant who stated that she was not based in the UK. The global press release was not issued in the UK.

Roche noted that the IMAGE trial was the first radiographic trial using rituximab in combination with MTX in RA patients who had previously been naïve to traditional DMARDs. Up until now rituximab had only shown a disease modifying effect via radiographic measurements in patients who had failed to respond to anti-TNF therapies.

Roche noted that IMAGE was a Phase III, randomized, controlled, double-blind trial involving 755 patients to evaluate the safety and efficacy of rituximab in combination with MTX compared with MTX alone, in MTX-naïve patients with active RA. Patients in the rituximab arms were either treated with 2 x 1000mg or 2 x 500mg. At week 24 patients with disease activity score (DAS) >2.6 received a second course of rituximab. Those with DAS <2.6 were re-treated if and when their DAS exceeded 2.6. The primary endpoint was the change from screening in the modified radiographic total sharp score (mTSS) at week 52.

In patients treated with 2 x 1000mg rituximab and MTX, the baseline to one year data showed a significantly smaller change (0.359) in mean mTSS compared with patients on MTX alone (1.079; p=<0.001) – a lower progression of joint damage. By week 52, 65% of these patients achieved a 50% improvement in symptoms (ACR50), while 47% had achieved a 70% improvement (ACR70), compared with 42% and 25% on MTX alone.

Roche submitted that it was of particular clinical interest that in the second half of the study (between 6 and 12 months) there was near complete inhibition of further joint damage in patients treated with rituximab plus MTX (0.03 mean mTSS vs 0.38 mean change for MTX alone; p=0.0013). This finding was extremely valuable in terms of significantly inhibiting the progression of the destructive nature of rheumatoid arthritis and thus limiting the impact of the disease on a patient's ability to undertake normal physical activity. By limiting early damage by pharmacological intervention it was known that the long term outcome for patients could be significantly improved.

Given that this was the first time that an anti CD20 medicine had demonstrated such effects in this early RA patient population it was deemed to be newsworthy both medically and financially and thus Roche legimately issued a press release to both the consumer and medical press. This was evidenced by the statement made by the President Elect of EULAR a globally respected academic rheumatologist who independently stated to The Daily Telegraph that 'This is important news'. Roche had submitted a licence application for the use of rituximab in this patient population.

Roche considered that the press release had been written and issued in line with the principles outlined in Clause 22 of the Code. The release was non promotional, factually correct regarding the outcome of the study, placed both the efficacy and safety of the medicine in a balanced way, included a paragraph on the adverse event profile and did not use language that could be considered to encourage members of the public to ask their health professional to prescribe rituximab.

With regard to Clause 12.1, the press release was written, reviewed and certified as a non promotional piece of material in line with established internal Roche UK standard operating procedures. Roche strongly refuted any suggestion that it either directly, or via a third party, used this press release as a method of disguised promotion. Roche noted that Clause 3.2 stated that the promotion of a medicine must be in accordance with the terms of its marketing authorization. Roche submitted that the press release reported the outcome of a pivotal clinical development trial and thus its content was outside the current marketing authorization, however as stated previously, it was non promotional and was financially and medically newsworthy. Similarly it was clearly stated in the main body of the release that rituximab was not currently licensed for use in early RA. Overall Roche considered it was produced in line with Clause 22 and Roche strongly refuted that the press release was in breach of Clause 3.2.

Roche submitted that given the information outlined above it did not consider that the production and release of this material to be in breach of either Clauses 9.1 or 2.

Roche was concerned that the complainant was dissatisfied about newspapers publishing stories about medicine development and considered these to be marketing related material. However Roche was very careful to ensure only financially and medically newsworthy information was put into the public domain. Roche did not accept that the press release pushed medicines to the public, nor did it accept that it made no mention of the side effects, it was a balanced piece of information that was of press interest and produced in line with the principles set out in the Code.

PANEL RULING

The Panel noted that complaints about articles in the press were judged on the information provided by the pharmaceutical company or its agent to the journalist and not on the content of the article itself. Clause 22.1 prohibited the advertising of prescription only medicines to the general public. Clause 22.2 permitted information to be supplied directly or indirectly to the general public but such information had to be factual and provided in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their health professional to prescribe a specific medicine.

The Panel noted that although the complainant had complained about articles in the UK press, she had provided a copy of the global press release. The global press release had not been issued in the UK. The UK press release detailed results from the IMAGE trial as presented at the EULAR conference. It was stated that 30.5% of the RA patients taking rituximab and MTX achieved remission vs 12.5% of those taking MTX alone. The Panel considered that the UK press release was written in a factual, balanced and non promotional manner. The press release clearly stated that rituximab was not licensed for early RA. A short paragraph also referred to side effects such as hypertension, nausea and upper respiratory tract infections. It was stated that as with all RA therapies, a small proportion of more serious side-effects were seen.

The Panel did not consider that the press release raised unfounded hopes of successful treatment or was misleading with respect to the safety of the product.

The Panel considered that any good news story about a medicine would have an inevitable positive impact but nonetheless it did not consider that statements had been made for encouraging patients to ask their health professional to prescribe rituximab. The Panel ruled no breach of Clause 22.2 of the Code. The press release was not an advertisement *per se* for rituximab and nor was it disguised promotion; no breach of Clauses 22.1 and 12.1 were ruled. The Panel noted that rituximab was not indicated for use in early RA however it did not consider that the press release promoted an unlicensed indication. No breach of Clause 3.2 was ruled. In the Panel's view Roche had not failed to maintain high standards and no breach of Clause 9.1 of the Code was ruled. Given the rulings above, there could be no breach of Clause 2 and the Panel ruled accordingly.

Complaint received **16 June 2009**

Case completed **22 July 2009**