CASE AUTH/1915/11/06

ASTRAZENECA v NOVARTIS

Femara leavepiece and press release

AstraZeneca complained about a Femara (letrozole) leavepiece issued by Novartis. AstraZeneca alleged that claims that Femara offered protection against increased risk in patients with lymph node positive disease were misleading as they reported only the positive aspect of the trial data, without reporting results for women who had lymph node negative disease. Lymph node status was routinely used to define the risk of recurrence in breast cancer once primary treatment had been administered. It was not clear in the leavepiece that there was currently no evidence of Femara's improved efficacy over tamoxifen in patients with lymph node negative disease. Where a medicine was perceived to be more 'potent' in preventing cancer recurrences in 'higher risk' patients ie node positive patients, there could also be a perception that it would have enhanced benefit in lower risk patients, ie node negative patients. Thus, this lack of clarification might encourage use of Femara in not just node positive patients but also in node negative patients. AstraZeneca had anecdotal evidence that certain clinicians and hospital trusts advocated the use of Femara in all patients requiring an aromatase inhibitor, due to perceived improved potency.

AstraZeneca alleged that claims that Femara offered protection against increased risk in patients who had had previous chemotherapy, were similarly misleading. Patients who had chemotherapy as part of their primary treatment were again perceived to be at higher risk of breast cancer recurrence. The most recent data indicated that Femara was no more effective than tamoxifen in women who had not had previous chemotherapy. With reference to the argument above, making claims only on the positive aspects of the data might encourage clinicians to prescribe Femara in groups of patients who might not benefit but might in consequence suffer unnecessarily from serious adverse events.

The Panel considered that claims about Femara and a woman's nodal status clearly referred to data in node-positive women. There was no implication that the data also applied to lymph node-negative disease. The Panel did not accept that in this instance it was misleading to only refer to the positive aspect of the trial. The relevant subgroup analysis was pre-planned. The data for node-negative disease showed no statistically significant difference between tamoxifen and letrozole. The Panel did not consider that the claims in question were misleading as alleged. No breach of the Code was ruled. This ruling was appealed by AstraZeneca.

Similarly the Panel considered that claims about Femara and previous chemotherapy clearly referred to data in patients who had had previous chemotherapy. There was no implication that the data also applied to patients who had not had chemotherapy. The Panel did not accept that in this instance it was misleading to only refer to the positive aspect of the trial. The relevant subgroup analysis was pre-planned. The data for patients who had not had chemotherapy showed no statistically significant difference between tamoxifen and letrozole. The Panel did not consider that the claims in question were misleading as alleged. No breach of the Code was ruled. This ruling was appealed by AstraZeneca.

Upon appeal by AstraZeneca the Appeal Board noted that all of the claims at issue were referenced to the BIG 1-98 study. The results of that study showed that overall disease free survival was significantly greater in the Femara group than in the tamoxifen group (p=0.003). A number of subgroup analyses were performed; the resulting Forest plot showed that the confidence intervals all overlapped a central line demonstrating that none of the subgroups differed significantly from the overall treatment effect in the whole population. No statistical correction had been applied to the results to allow for multiple subgroup analysis.

The first bar chart in the leavepiece at issue showed that for the whole BIG 1-98 study group there was a 19% decrease in recurrences in the Femara group (p=0.003). Two subsequent bar charts showed a 29% decrease in recurrences in node-positive women (p=0.0002) and a 28% decrease in recurrences in those women who had had previous chemotherapy (p=0.02). The differences between 19% and 29% and 28% had been emphasised by proportionately larger downward arrows. The Appeal Board noted its comments above and considered that, given the statistical analysis of the results, there was no way of knowing if the results for the node-positive women and for those who had had previous chemotherapy were truly different from the whole patient population such that there was additional benefit from treatment for these two groups.

The Appeal Board considered that the DFS data from the BIG 1-98 study had been presented in such a way as to imply an increased benefit for Femara in node-positive women and in those who had had previous chemotherapy. Such benefits were unproven. The Appeal Board thus considered that the impression from the leavepiece was misleading as alleged. Breaches of the Code were ruled. The appeal was successful.

AstraZeneca was concerned that there were no safety statements regarding potential serious adverse events within the main body of the leavepiece to provide an

adequate benefit/risk profile of Femara. Although it was claimed that 'Overall FEMARA was generally well tolerated compared with tamoxifen', there were no statements within the leavepiece to clarify what the potential risks were of taking Femara, in particular that women on Femara could anticipate a reduction in bone mineral density, which might increase fracture risk. Given that postmenopausal early breast cancer patients who had received their primary treatment(s) were essentially well, omission of such a potentially serious side effect was misleading.

The Panel noted that the leavepiece did not mention the potential risks of taking Femara. Details of the side effects were given in the prescribing information. The leavepiece stated that 'Overall Femara was generally well tolerated compared with tamoxifen'. The Panel did not consider that the omission of a reference to possible reductions in bone mineral density was such that there was a failure to provide an adequate benefit/risk profile of Femara or that it was misleading as alleged. The Panel ruled no breach of the Code.

AstraZeneca alleged that the claim 'Femara is now the first and only [aromatase inhibitor] licensed for treatment across the entire breast cancer treatment spectrum' in a Novartis press release could not be justified. The word 'entire' was misleading as it could easily be misconstrued as Femara having a marketing authorization for all breast cancer treatment settings which was not so.

The Panel considered that the claim was misleading. Femara was not licensed across the entire breast cancer spectrum; the table of licensed indications in the press release showed that Femara was not licensed for use within five years of surgery, switching from tamoxifen (adjuvant switch). The Panel considered that the press release was thus misleading and not capable of substantiation. Breaches of the Code were ruled.

AstraZeneca UK Limited complained about the promotion of Femara (letrozole) by Novartis Pharmaceuticals UK Ltd. At issue was a leavepiece (ref FEM 05000083). AstraZeneca supplied Arimidex (anastrozole) and Nolvadex-D (tamoxifen).

1 LEAVEPIECE

COMPLAINT

AstraZeneca referred to four claims.

1 'FEMARA - protection against increased risk in specific patient subgroups' followed by a bar chart headed: 'DFS [disease free survival] events in node positive women'.

2 'FEMARA - protection against increased risk in specific patient subgroups' followed by a bar chart headed: 'DFS events in women who had previous chemotherapy'.

3 'FEMARA - for women at increased risk of recurrence eg node-positive and/or previous chemotherapy'.

4 'Overall FEMARA was generally well tolerated compared with tamoxifen'.

AstraZeneca alleged that claims 1 and 3 were misleading as they reported only the positive aspect of the trial data, without reporting results for women who had lymph node negative disease. Lymph node status was routinely used by breast cancer surgeons and oncologists to define the risk of recurrence in breast cancer once primary treatment had been administered and accordingly, lymph node positivity was widely regarded as a predictive factor for a higher risk of cancer recurrence. It had not been made clear within the leavepiece that there was currently no evidence at present of Femara's improved efficacy over tamoxifen in patients with lymph node negative disease. Where a medicine was perceived to be more 'potent' in preventing cancer recurrences in 'higher risk' patients ie node positive patients, there could also be a perception that it would have enhanced benefit in lower risk patients, ie node negative patients. Thus, this lack of clarification might encourage use of Femara in not just node positive patients but also in node negative patients. Already, AstraZeneca had anecdotal evidence that certain clinicians and hospital trust guidelines advocated the use of Femara in all patients requiring an aromatase inhibitor, due to perceived improved potency.

Similarly AstraZeneca alleged in claims 2 and 3 that Femara offered protection against increased risk in patients who had had previous chemotherapy, were misleading as they reported only on the positive aspects of the trial data, without reporting on the most recent trial data for women who did not have chemotherapy. Patients who had chemotherapy as part of their primary treatment were again perceived to be at higher risk of breast cancer recurrence. The most recent data indicated that Femara was no more effective than tamoxifen in women who had not had previous chemotherapy. With reference to the argument above, making claims only on the positive aspects of the data might encourage clinicians to prescribe Femara in groups of patients who might not benefit but might in consequence suffer unnecessarily from serious adverse events.

Breaches of Clauses 7.2, 7.3 and 7.10 of the Code were alleged.

AstraZeneca was concerned that there were no safety statements regarding potential serious adverse events within the main body of the leavepiece to provide an adequate benefit/risk profile of Femara. Although page 4 of the leavepiece claimed that, 'Overall Femara was generally well tolerated compared with tamoxifen', there were no statements within the leavepiece to clarify what the potential risks were of taking Femara. Section 4.4 of the Femara summary of product characteristics (SPC) stated that women on Femara could anticipate a reduction in bone mineral

density, which might increase fracture risk and that bone mineral density assessment should be carried out during treatment. Given that postmenopausal early breast cancer patients who had received their primary treatment(s) were essentially well, omission of such a potentially serious side effect was misleading. Breaches of Clauses 7.2 and 7.10 of the Code were alleged.

In summary the claims were misleading to health professionals due to the unbalanced presentation of the data. There were also insufficient safety statements within the leavepiece to enable a balanced evaluation of the safety/risk profile.

RESPONSE

Novartis noted that the first page of the leavepiece clearly summarised some of the key data from the BIG 1-98 study at an interim analysis published in the New England Journal of Medicine (NEJM). The analysis of data from 8010 women with breast cancer, treated with either tamoxifen or Femara and followed for a median of 25.8 months was that, compared with taxoxifen, adjuvant treatment with Femara reduced the risk of recurrent disease, especially at distant sites.

A number of pre-planned subgroup analyses were also performed at this time point including a comparison of those who had and had not received previous chemotherapy and also a comparison of those women with disease known to have involved lymph nodes with those who had not or whose nodal status was unknown at study entry.

These pre-planned analyses demonstrated that there was a reduced recurrence of disease in patients treated with Femara who had either received previous chemotherapy or who had node positive disease. This difference was statistically significant and when expressed as a hazard ratio, the risk in these groups was 0.77 and 0.71 indicating a reduction in risk of 23% and 29% respectively for women in these groups treated with Femara compared with those treated with tamoxifen. In women who had not received previous chemotherapy or had no nodal disease or unknown nodal status, a statistically significant difference was not seen. However, overall, there was a statistically significant difference between the two treatments in favour of Femara.

In these 'high risk' groups, recurrences were more common and so a reduction in the incidence of recurrence would be more easily seen over this time period. One explanation for the lack of statistically significant difference between the treatments in the 'low risk' (node negative and no prior chemotherapy) groups might be that the lower rate of recurrence overall meant that a difference was harder to demonstrate at this earlier timepoint.

It was important to note that Femara was not suggested to be inferior to tamoxifen with regards to efficacy in the low-risk groups of women in this study and the results suggested that there might even still be an advantage in efficacy, which might have revealed itself had the sample size been greater, as could clearly be seen in the 'Forest plots' in the NEJM paper.

In summary, Novartis believed that the data supported promotion of the use of Femara in these high risk subgroups of node positive women and those who had received previous chemotherapy. Novartis did not accept that it had promoted the use of Femara in women who were node negative or who had not received previous chemotherapy although, unlike some aromatase inhibitors, Femara was licensed in both node positive and node negative disease. It was therefore not unexpected that some clinicians advocated its use in patients regardless of nodal status as observed by AstraZeneca. Finally Novartis did not accept that prescribing Femara instead of tamoxifen in these 'low risk groups' in any way prejudiced patient care. As concluded in the NEJM paper 'our results indicate that Letrozole is an effective option for standard adjuvant therapy, with a relatively favorable safety profile in postmenopausal women with endocrine-responsive breast cancer'.

Novartis disagreed that additional safety statements regarding treatment induced osteoporosis should be included in the leavepiece. This association, as for all common and serious adverse events, was included in the prescribing information. In this particular study, those patients treated with Femara experienced less throboembolic events, lower rate of vaginal bleeding, fewer endometrial biopsies and fewer invasive endometrial cancers than those women treated with tamoxifen. The authors concluded that Femara had a 'relatively favourable safety profile' and so the description of 'well tolerated' was not inconsistent with that.

PANEL RULING

The Panel considered that claim 1 (Femara – protection against increased risk in specific patient subgroups: DFS events in node positive women) and claim 3 (Femara – for women at increased risk of recurrence eg node-positive and/or previous chemotherapy) clearly referred to data in node-positive women. There was no implication that the data also applied to lymph node-negative disease. The Panel did not accept that in this instance it was misleading to only refer to the positive aspect of the trial. The relevant subgroup analysis was pre-planned. The data for node-negative disease showed no statistically significant difference between tamoxifen and Femara. The Panel did not consider that the claims in question were misleading as alleged. No breach of Clauses 7.2, 7.3 and 7.10 was ruled. This ruling was appealed by AstraZeneca.

The Panel considered that claim 2 (Femara – protection against increased risk in specific patient subgroups: DFS events in women who had previous chemotherapy) and claim 3 (Femara – for women at increased risk of recurrence eg node-positive and/or previous chemotherapy) clearly referred to data in patients who had had previous chemotherapy. There was no implication that the data also applied to patients who had not had chemotherapy. The Panel did

not accept that in this instance it was misleading to only refer to the positive aspect of the trial. The relevant subgroup analysis was pre-planned. The data for patients who had not had chemotherapy showed no statistically significant difference between tamoxifen and Femara. The Panel did not consider that the claims in question were misleading as alleged. No breach of Clauses 7.2, 7.3 and 7.10 was ruled. This ruling was appealed by AstraZeneca.

The Panel noted that the leavepiece did not mention the potential risks of taking Femara. Details of the side effects were given in the prescribing information. The leavepiece stated that 'Overall Femara was generally well tolerated compared with tamoxifen'. The Panel did not consider that the omission of a reference to possible reductions in bone mineral density was such that there was a failure to provide an adequate benefit/risk profile of Femara or that it was misleading as alleged. The Panel ruled no breach of Clauses 7.2 and 7.10. This ruling was not appealed.

APPEAL BY ASTRAZENECA

AstraZeneca noted that all three claims related to the use of subgroups as reported in the BIG 1-98 study. AstraZeneca alleged that it was inappropriate and misleading to promote findings of subgroup analyses which took into account sub-populations of the total study population and were distinct from secondary end-point analyses, which analysed different outcomes in the total study population, out of context of the main study. Outlined below were details of the subgroup analyses performed in the BIG 1-98 study and the hazards of misusing subgroup analyses, which in this case misrepresented the views of the study authors. These findings highlighted the need for caution in interpreting subgroup analyses, even in large trials. No subgroups showed significantly different relative efficacy; in particular no significant heterogeneity was observed by nodal involvement status or progesterone receptor status (Coates *et al* 2007).

AstraZeneca noted that the BIG 1-98 study was prospectively designed to assess the benefit of Femara versus tamoxifen in the overall population of breast cancer patients. The primary end point was powered to show an overall effect in DFS and patients were stratified by centre and use of chemotherapy. Therefore the overall objective of this study was not to show benefits in subgroups. It was well accepted that drawing conclusions based on subgroup analyses could be problematic and needed to be placed in context (Altman *et al*, 1996, Mathews *et al* 1996). Altman *et al* highlighted their concerns with this approach stating: 'Exploratory examination of many such subgroups is almost certain to throw up some spurious significant interactions and in practice we cannot tell if a specific interaction is real or spurious'. This concern was also reflected in well-established regulatory guidelines on this issue, the Committee for Proprietary Medicinal Products (CPMP) produced in September 2002 a guidance document for managing multiplicity issues in clinical trials. The Committee emphasised the need for clarification and caution by stating:

'Multiplicity of inferences is present in virtually all clinical trials. The usual concern with multiplicity is that, if it is not properly handled, unsubstantiated claims for the effectiveness of a drug may be made as a consequence of an inflated rate of false positive conclusions. For example, if statistical tests are performed on five subgroups, independently of each other and each at a significance level of 2.5% the chance of finding at least one false positive statistically significant test increases to 12.5%.'

AstraZeneca alleged that the initial publication of the BIG 1-98 study recognised the caution that needed to be applied in these circumstances. Such caution was still required even if such subgroup analyses were pre-planned. The discussion section outlined the different findings in subgroups between the ATAC study (an AstraZeneca study of anastrozole in a similar setting) and the BIG 1-98 study and discussed the fact that the ATAC study subgroup analyses suggested preferential benefits in patients with progesterone receptor negative disease. This finding was, quite rightly, interpreted with caution and had subsequently not been confirmed in other studies. AstraZeneca had therefore not promoted on subgroup data from the ATAC study on this basis. The BIG 1-98 study concluded by clearly stating: 'These findings highlight the need for caution in interpreting subgroup analyses, even in large trials'.

In this case AstraZeneca alleged that it was inappropriate to use subgroup data to infer a treatment benefit and that this contradicted the opinions of the authors. It was also inappropriate to highlight benefits seen in subgroups without clarifying the uncertainty attached to such findings.

Existing evidence (including the BIG 1-98 study data) was reviewed by a recent National Institute for health and Clinical Excellence (NICE) technology assessment on hormonal therapies for the adjuvant treatment of early oestrogen-receptor-positive breast cancer, where it was concluded that:

'However, because of the lack of definitive evidence on the relative clinical and cost effectiveness of the use of the aromatase inhibitors in different risk groups, the Committee did not feel able to issue guidance on the relative cost effectiveness of the aromatase inhibitors for the different subgroups.'

AstraZeneca alleged that these examples confirmed the generally held view that subgroup analyses must be treated with caution and did not provide definitive evidence of a clinical effect.

AstraZeneca submitted that subgroup analyses could be useful in large clinical trials. Analysis could highlight certain patient groups that might be inconsistent with the overall treatment effect. This testing of heterogeneity was well recognised in medical statistics. When used in this way subgroup analysis might be helpful in establishing a hypothesis for

further evaluation. This was a valid and appropriate use of subgroups as outlined by Altman *et al*, Cuzick (2005) and the CPMP guidance. The most recent (51-month median follow up) BIG 1-98 publication clearly outlined this appropriate use of the subgroup analyses:

'We explored various protocol defined subgroups to identify whether there was any apparent difference in the relative efficacy of letrozole on DFS compared with the overall benefit observed. No subgroups showed significantly different relative efficacy; in particular no significant heterogeneity was observed by nodal involvement status or progesterone receptor status (Fig 3B)' (Coates *et al*).

AstraZeneca alleged that it was clear, therefore, that the authors of the BIG 1-98 study did not place clinical importance on the statistically significant finding in the node-positive or chemotherapy group, and indeed had correctly utilised appropriate subgroup analyses to demonstrate that nodal status did not demonstrate heterogeneity. In particular they did not refer to the statistically significant findings in figure 3B, the subgroup table, reflecting only that no subgroups demonstrated heterogeneity. Heterogeneity testing examined whether a treatment worked better in some subgroups compared with others. Although AstraZeneca accepted that this article was published after the original complaint, it further reinforced its original concern around the inappropriate and misleading claims that Novartis had formed from subgroup data. It was therefore, appropriate to introduce this information as further evidence of its concerns.

AstraZeneca submitted that it had provided review articles which clearly outlined how subgroup analyses should be assessed. On the specific issue of node-positive versus node-negative patients, as outlined in its complaint, in order to test for possible interaction in node-positive women, the more appropriate analysis would have been to test for interaction between the node-negative population and the node-positive population. It was this analysis that would determine whether Femara demonstrated efficacy benefits in node-positive women over node-negative women. These analyses had been performed and led to the BIG group to conclude: 'No subgroups showed significantly different relative efficacy; in particular no significant heterogeneity was observed by nodal involvement status or progesterone receptor status'.

AstraZeneca noted the letter from Cuzick, which eloquently outlined the confusions and misinterpretations that occurred from Forest plot analyses and explained how the confusion could arise from misinterpretation of the 'bold line' depicted at the 'no effect' level. The BIG group had correctly utilised the Forest plot to make an appropriate conclusion on the subgroup analysis.

AstraZeneca noted that Novartis had submitted that the analyses were pre-planned. Whilst it was beneficial to pre-plan such analyses it did not exempt them from the issues of multiplicity, as outlined by the CPMP guidance and the articles by Altman *et al*. Furthermore, prospective planning of subgroup analyses did not provide an exemption to carrying out appropriate adjustments such as heterogeneity tests. They also referred to the authors' endorsement of Femara, but did not highlight the authors' concerns around the use of subgroups. Finally, AstraZeneca alleged that Novartis' submission suggesting an explanation for the benefit being observed in high-risk patients where it claimed that 'high-risk' patients' disease recurred earlier and therefore it was easier to show the benefits in these women, further supporting the argument that those apparent differences created by subgroup analyses, did not relate to true clinical differences between subgroups.

In summary, AstraZeneca alleged that the leavepiece was in breach of the Code as it represented selected subgroup analyses as clinical evidence when such analyses were insufficient to provide definitive evidence of a clinical effect and misrepresented the views of the authors.

More specifically:

- The authors of BIG 1-98 clearly highlighted the concerns of subgroup analyses with the statement, 'No subgroups showed significantly different relative efficacy'. The leavepiece was therefore inconsistent with the authors' views.

- The interpretation of the analysis had been misrepresented and dissemination of such information posed the risk of inappropriate conclusions being made by health professionals, which might affect treatment of patients.

- It was inappropriate to conclude from the data, that particular subgroups of patients demonstrated heterogeneity (ie differed from the overall population) within the BIG 1-98 population and to suggest that there were differential benefits for Femara in node-positive patients.

For these reasons, AstraZeneca alleged that it was inappropriate to use subgroup data to make definitive claims of efficacy, and even more so without representing the data in a balanced manner. Therefore the leavepiece breached Clauses 7.2, 7.3 and 7.10.

COMMENTS FROM NOVARTIS

Novartis noted that AstraZeneca continued to assert that promotional claims could not be based on subgroup analyses and that the breaches of the Code it alleged all related to this assertion. Novartis fundamentally disagreed with this and maintained that appropriate use of subgroup analyses provided additional information to prescribers on the activity of a medicine and allowed them to be better informed when deciding on the most appropriate management of their patients.

Novartis noted that the leavepiece was used to reinforce messages following a full and frank discussion with the health professional on the data

contained. The flow of the item first identified the design of the BIG 1-98 study and the primary outcome. Only then was there a discussion of the particular pre-planned subgroup analyses within the context of the main study.

Novartis noted how AstraZeneca had interpreted the CPMP paper, 2002, on the issue of multiplicity issues in clinical trials. AstraZeneca had quoted the opening statement of the guidance that cautioned about the inappropriate use of data generated within clinical trials, without appropriate and robust statistical prior consideration to support claims.

Novartis agreed that 'data dredging' and retrospective analyses to support sophistic arguments could never be condoned. However the paper went on to discuss the analysis of subgroup data according to a pre-defined statistical plan. The guidance stated: 'in general, multiple analyses of varying subsets of subjects or with varying measurements for the purpose of investigating the sensitivity of the conclusions drawn from the primary analysis should not be subjected to adjustment for type 1 error. The main purpose of such analyses was to increase confidence in the results obtained from the primary analysis'.

The paper then went on to specifically discuss where claims could be made from the analysis of secondary variables and stated: 'secondary variables may be related to secondary objectives that become the basis for an additional claim, once the primary objective has been established'.

Novartis submitted that the primary endpoint of the BIG 1-98 study was to compare treatment with Femara and tamoxifen and the effect on DFS. The result of this primary analysis was that DFS was significantly greater in the Femara group than the tamoxifen group (hazard ratio for the primary end point, 0.81; 95 percent confidence interval, 0.70 to 0.93; P = 0.003 by the log-rank test). Therefore with the primary objective established, it was then appropriate and in line with the CPMP guidelines to provide additional granularity by performing pre-planned subgroup analyses.

Novartis submitted therefore that the additional analysis demonstrated that there was a significant improvement in DFS (as demonstrated in a statistically and clinically significant reduction in DFS events in the Femara group when compared with the tamoxifen group) in groups with node-positive disease or who had received prior chemotherapy which was important information for physicians in making management decisions. These groups represented women with more aggressive disease. It was likely that the lack of a demonstrable difference between the treatment arms in those groups with node-negative/unknown disease or who had not received prior chemotherapy was driven by the lower rate of events in either group and that a larger sample size would be needed to show this difference.

Novartis submitted that AstraZeneca had referred to the most recent analysis of data from the BIG-1-98 study, Coates *et al* that was presented at the 2006 meeting of the European Society of Medical Oncology (ESMO) and would be published in the near future. This publication reported a subsequent analysis of a subset of patients from the whole study population at a median follow-up of 51 months. The population considered for this analysis was only around 62% of the total population (4922 out of total of 8028). The paper showed that there was still an improvement in DFS seen in those women treated with Femara over those treated with tamoxifen. In the subgroup analyses this improvement was still seen in the node-positive subgroup (HR 0.77, 95% CI 0.64-0.92) and those women who had received prior chemotherapy (HR 0.74, 95% CI 0.56-0.97). This was consistent with the results seen in the previous analysis of the whole population in the 2005 NEJM paper. The quote regarding lack of heterogeneity referred to the consistency of superiority of Femara over tamoxifen in all subgroups although this was not statistically significant in the node-negative and chemotherapy-naïve groups.

In conclusion Novartis did not accept that the arguments presented by AstraZeneca in relation to the interpretation of subgroup analyses should alter the original ruling. The leavepiece was not in breach of the Code as alleged.

FURTHER COMMENTS FROM ASTRAZENECA

AstraZeneca noted that Novartis had extracted details from the CPMP guidance document it had initially highlighted. In particular Novartis used the wording from section 2.2. AstraZeneca concurred exactly with Novartis' use of this extract. However AstraZeneca was concerned that Novartis had not correctly interpreted this guidance. The paragraph clearly stated: 'The main purpose of such analyses is to increase confidence in the results obtained from the primary analysis'.

AstraZeneca submitted that the CPMP guidance was clear with regard to use of subgroups, which should be analysed to ensure the overall result seen was consistent across different sub-populations, and it had outlined the appropriate interpretation previously.

AstraZeneca further noted and concurred with Novartis' use of a second extract from the CPMP guidance section 3.2, that: 'secondary variables may be related to secondary objectives that become the basis for an additional claim, once the primary objective has been established'.

AstraZeneca was concerned that Novartis had misunderstood and misrepresented this guidance. Section 3.2 related to the use of secondary variables (endpoints). The primary variable for the BIG 1-98 study was DFS. Secondary variables in the BIG 1-98 study were overall survival, systemic disease free survival, and safety. AstraZeneca therefore agreed that Novartis might promote benefits seen for these endpoints, especially as the primary endpoint was achieved. However this paragraph did not relate to subgroups, which were covered in section 4 and they had therefore misrepresented this regulatory guidance.

AstraZeneca agreed that secondary endpoints could be valuable in studies of this nature, but maintained that a different approach was required for subgroups.

AstraZeneca also noted Novartis' rationale for the benefits seen in these two subgroups, and in particular the fact that these patients were high risk and therefore benefits might be seen earlier. A similar study design utilising Arimidex (another aromatase inhibitor) had been published in 2002 (ATAC). The ATAC and BIG 1-98 studies had shown identical benefits in their primary endpoint, DFS. Interestingly, if one extracted subgroups from this study it was women who did not have chemotherapy, and those with node-negative disease, that benefited preferentially. These women were low risk and therefore showed contradictory findings to the BIG 1-98 study. This again highlighted the pitfalls in interpreting subgroups in this way.

Finally AstraZeneca was concerned to see Novartis' misrepresentation of the authors' statement from the 2007 publication. The authors clearly stated: 'No subgroups showed significantly different relative efficacy; in particular, no significant heterogeneity was observed by nodal involvement status or progesterone receptor status'.

Novartis had correctly outlined in its response that: 'The quote regarding lack of heterogeneity refers to the consistency of superiority of Femara over tamoxifen in all subgroups'. In order for this to be the case it could not then be concluded that there were subgroups for whom a greater benefit was observed. By virtue of the statements above the subgroups were showing consistent benefits.

Finally AstraZeneca highlighted an issue with the supposed subgroup benefit. If one followed Novartis' line of reasoning the BIG 1-98 study showed that women with ER-positive disease gained no benefit from Femara and AstraZeneca knew this to be wrong. This further illustrated the pitfalls in interpreting subgroups in this way.

APPEAL BOARD RULING

The Appeal Board noted that all of the claims at issue were referenced to the BIG 1-98 study. The results of that study showed that overall DFS was significantly greater in the Femara group than in the tamoxifen group (p=0.003). A number of subgroup analyses were performed; the resulting Forest plot showed that the confidence intervals all overlapped a central line demonstrating that none of the subgroups differed significantly from the overall treatment effect in the whole population. No statistical correction had been applied to the results to allow for multiple subgroup analysis.

The first bar chart in the leavepiece at issue showed that for the whole BIG 1-98 study group there was a 19% decrease in recurrences in the Femara group (p=0.003). Two subsequent bar charts showed a 29% decrease in recurrences in node-positive women (p=0.0002) and a 28% decrease in recurrences in those women who had had previous chemotherapy (p=0.02). The differences between 19% and 29% and 28% had been emphasised by proportionately larger downward arrows. The Appeal Board noted its comments above and considered that, given the statistical analysis of the results, there was no way of knowing if the results for the node-positive women and for those who had had previous chemotherapy were truly different from the whole patient population such that there was additional benefit from treatment for these two groups.

The Appeal Board considered that the DFS data from the BIG 1-98 study had been presented in such a way as to imply an increased benefit for Femara in node-positive women and in those who had had previous chemotherapy. Such benefits were unproven. The Appeal Board thus considered that the impression from the bar charts and the claims at issue 'Femara - protection against increased risk in specific patient subgroups: DFS events in node-positive women', 'Femara - protection against increased risk in specific patient subgroups: DFS events in women who had previous chemotherapy' and 'Femara - for women at increased risk of recurrence eg node-positive and/or previous chemotherapy' was misleading as alleged. Breaches of Clauses 7.2, 7.3 and 7.10 were ruled in respect of each claim. The appeal was successful.

2 PRESS RELEASE

COMPLAINT

AstraZeneca alleged that the claim 'Femara is now the first and only [aromatase inhibitor] licensed for treatment across the entire breast cancer treatment spectrum - before surgery, directly post-surgery, after five years of standard tamoxifen treatment and in advanced cancer' could not be justified. The word 'entire' was misleading as it could easily be misconstrued as Femara having a marketing authorization for all breast cancer treatment settings. Other aromatase inhibitors such as Arimidex and Aromasin were licensed for the adjuvant treatment of postmenopausal women who had had 2-3 years of initial tamoxifen. However, Novartis did not have a marketing authorization for use of Femara in this setting and thus the claim was not justified. Furthermore, the prescription of aromatase inhibitors after 2-3 years of tamoxifen was an evidence-based treatment strategy that had now been approved by NICE and was therefore not a refinement within the primary adjuvant setting. Health professionals and the public could be misled into thinking that Femara could also be used for this treatment setting. Breaches of Clauses 3.2, 7.2, 7.3, 7.4 and 20.2 of the Code were alleged.

RESPONSE

Novartis disagreed with AstraZeneca's interpretation. The claim referred to the indications which covered the possible uses of an aromatase inhibitor in the treatment of women with breast cancer. Although the use of an aromatase inhibitor in the adjuvant setting after a

period of treatment with tamoxifen had been listed as an additional indication for some aromatase inhibitors, this did not represent a fundamentally different use of these agents. Indeed, the NICE publication divided treatment into 'surgical treatment and adjuvant treatment after surgical removal of the primary cancer'. It described primary adjuvant use and switch therapy as different 'treatment strategies' rather than fundamentally different treatment settings.

The press release clearly presented the licensed indications for the aromotase inhibitors in tabular format leaving the reader in no doubt about the licensed use of the products. In addition the full licensed indications for Femara were listed in the main body of the text.

Femara was the only aromatase inhibitor licensed before surgery, directly post-surgery, after five years of standard tamoxifen treatment and in advanced cancer; therefore it was not unjustified to make this claim.

PANEL RULING

The Panel considered that the claim was misleading. Femara was not licensed across the entire breast cancer spectrum; the table of licensed indications in the press release showed that Femara was not licensed for use within five years of surgery, switching from tamoxifen (adjuvant switch). The Panel considered that the press release was thus misleading and not capable of substantiation. Breaches of Clauses 7.2, 7.3, 7.4 and 20.2 were ruled.

Complaint received	**10 November 2006**
Case completed	**13 March 2007**