CASE AUTH/3256/10/19

ANONYMOUS COMPLAINANT V NOVARTIS

Promotion of Kisqali

An anonymous individual, who described him/herself as a health professional, complained about a promotional leaflet (ref KIS19-CO25a) for Kisqali (ribociclib succinate) dated June 2019 issued by Novartis Pharmaceuticals UK Ltd. The complainant stated that the leaflet was provided at a conference for breast cancer.

Kisqali was indicated for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who had received prior endocrine therapy.

The complainant alleged that the leaflet was misleading, inaccurate and implied off-label use. The leaflet and campaign language was not responsible to patient care. In addition to the general comments, the complainant provided further information with regard to various parts of the leaflet which were considered as follows.

The detailed response from Novartis is given below.

1 Claim 'First-line Kisqali. The difference for patients is survival'

The complainant noted that whilst Kisqali had an indication for initial endocrine-based therapy, the overall survival data referenced was only for first-line in combination with an aromatase inhibitor in endocrine-sensitive patients. There was a separate cohort of first-line advanced breast cancer patients who were endocrine resistant (ie recurred on adjuvant therapy) who would not receive aromatase inhibitor-based therapy but a fulvestrant-based therapy instead, which was not included in this data set. The complainant alleged that the claim was misleading in intent.

In the Panel's view, first-line Kisqali, as referred to within the leaflet, could be seen as the use of Kisqali with either an aromatase inhibitor or fulvestrant as according to the Kisqali SPC each combination was indicated for initial endocrine-based therapy for the treatment of advanced breast cancer. The implication to readers might be that the overall survival data referred to within the leaflet applied to Kisqali in both combinations ie with either an aromatase inhibitor or fulvestrant which was not so.

The Panel noted that the leaflet at issue focussed on the results of a protocol-specified interim analysis of the key secondary endpoint of overall survival of the MONALEESA-7 trial data (Im *et al*). It noted Novartis' submission about the patients enrolled in the MONALEESA-7 trial. Patients received Kisqali and endocrine therapy, (goserelin plus either tamoxifen or a non-steroidal aromatase inhibitor); no patient received fulvestrant as a combination partner.

The Panel noted that there was no clear statement in the leaflet that the data related only to the first-line combination of Kisqali and an aromatase inhibitor and not fulvestrant and considered that this was misleading and, in relation to fulvestrant, was not capable of substantiation. The Panel therefore ruled breaches of the Code.

2 Claim 'Kisqali is the only CDK4/6 inhibitor to demonstrate significant overall survival benefit from a first-line phase III trial in a placebo-controlled trial of premenopausal women in combination with endocrine treatment as initial therapy'.

This claim appeared in a prominent orange band across the leaflet and the second half of the claim appeared in smaller type size than the first half. Below the band was a footnote 'Kisqali is not recommended to be used in combination with tamoxifen'.

The complainant alleged that due to the explanation at Point 1 above, 'the only' was not true because another CDK4/6 inhibitor had overall survival data in first-line endocrine resistant patients (in combination with fulvestrant, rather than an aromatase inhibitor). The complainant alleged that the claim was not factually accurate.

The complainant added that 'endocrine treatment' implied either aromatase inhibitor or fulvestrant, as these were the only two endocrine treatments listed in the Kisqali marketing authorization. However, the study did not include the fulvestrant combination, and instead included aromatase inhibitor or tamoxifen. The tamoxifen combination was not within Kisqali's marketing authorization. The complainant alleged that the claim was misleading and promoted off-licence use.

The Panel noted that the complainant did not identify the other CDK4/6 inhibitor or the study to which he/she referred to with regard to overall survival data in combination with fulvestrant. Novartis identified the CDK4/6 inhibitor with statistically significant overall survival data, as abemaciclib and the study as MONARCH 2 (Sledge *et al* 2019).

The Panel noted that like Kisqali, abemaciclib (Verzenios) was indicated for the treatment of women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who had received prior endocrine therapy.

The Panel noted that MONARCH 2 (Sledge *et al* 2019) was a double-blind, placebo-controlled phase III study of abemaciclib plus fulvestrant vs placebo plus fulvestrant in women with HR-positive, ERBB2 (formerly HER2)-negative advanced breast cancer who progressed during prior endocrine therapy. This included women who progressed during neoadjuvant or adjuvant endocrine therapy, within 12 months after adjuvant endocrine therapy, or whilst receiving first-line endocrine therapy for advanced breast cancer. The latter did not appear to be the subject of a subgroup analysis.

The Panel noted Novartis' submission with regard to the definition of primary and secondary endocrine resistance and what was meant by first-line and second-line treatment and that the MONARCH 2 population was a second-line population. It appeared to the Panel, however, that patients studied in MONARCH 2 were a mixture of first-line and second-line population in relation to advanced breast cancer. Outcome

survival data for the first line patients did not appear to have been reported separately. MONARCH 2 was on pre-, peri- and post-menopausal women and again the first-line population data for pre- and peri-menopausal patients did not appear to have been reported separately.

The Panel did not consider that the complainant had provided evidence to show that the claim that Kisqali was the only CDK4/6 inhibitor to demonstrate significant overall survival benefit from a first-line phase III trial in a placebo-controlled trial of pre-menopausal women in combination with endocrine treatment as initial therapy was misleading or incapable of substantiation. The Panel therefore ruled no breaches of the Code.

The Panel noted that there was no clear statement in the leaflet that the claims referred to were only in relation to Kisqali in combination with an aromatase inhibitor and not in combination with tamoxifen. In the Panel's view, there was, therefore, an implication that the data also referred to the combination with tamoxifen which was misleading and a breach of the Code was ruled.

Section 4.4 of the Kisqali SPC referred to QT interval prolongation results from MONALEESA-7 and included the statement that 'Kisqali is not recommended to be used in combination with tamoxifen (see sections 4.8 and 5.1'. There was a similar reference in Section 4.5. This meant that some of the data in MONALEESA-7 would not be in line with the Kisqali summary of product characteristics. The SPC included details about MONALEESA-7 and its results in Section 5.1.

The Panel noted that there was a difference between using data from a study, which included licensed and unlicensed doses to substantiate a specific, within licence claim, and general use for promotional purposes of a study that used licensed and unlicensed doses. The Panel did not consider that the reference to the overall MONALEESA-7 data which included the use of a combination that was inconsistent with the particulars listed in the Kisqali SPC necessarily meant that there had been a breach of the Code. The data referred to in the leaflet was that covered by the indication for Kisqali. There were no specific claims for the results with tamoxifen and the leaflet clearly stated that Kisqali was not recommended to be used in combination with tamoxifen. Whilst noting its ruling above that the leaflet could have been clearer that the claims within it were only in relation to Kisqali in combination with an aromatase inhibitor, the Panel did not consider that, taking all the circumstances into account, the leaflet was inconsistent with the SPC and thus ruled no breach of the Code.

3 Claim 'Kisqali is not recommended to be used in combination with tamoxifen'

The complainant noted that generally in the UK, 'recommended' was used to imply reimbursement (as the National Institute for health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC) used 'recommended' in technology appraisal documents to indicate a positive statement). The complainant noted, however, that not only did Kisqali not have reimbursement for use with tamoxifen, it did not have a marketing authorization to be used with tamoxifen. The complainant alleged that the claim was misleading and promoted off-licence use.

The Panel considered that the important point was that Kisqail was not recommended to be used with tamoxifen. It did not consider that the audience would interpret this statement in relation to reimbursement. The Panel did not consider that the statement, in itself, meant that the leaflet promoted Kisqali in a manner that was inconsistent with the SPC. No breach of the Code was ruled based on the narrow allegation.

4 Statement '[Overall survival] Data from MONALEESA – 2 and MONALEESA – 3 phase III trials in postmenopausal women with HR+/HER2 – advanced breast cancer are not available yet'

This statement appeared as a footnote to the claim considered at Point 2 above.

The complainant noted that the leaflet was disseminated five days after overall survival data for MONALEESA-3 was released at ESMO, as was overall survival data for abemaciclib in the same session, so the statement at issue was not accurate. The complainant acknowledged that it would take Novartis time to turn around a new document, but as the company knew in July that the data would be released at ESMO, it should not have sent an outdated and inaccurate leaflet to the meeting on 4 October – it should have been withdrawn.

The Panel considered that, at the time the leaflet was used, it was not true to state that the overall survival data from MONSLESSA-3 were not available. These were in the public domain prior to the meeting at which the leaflet was used. This data related to post-menopausal patients whereas the leaflet at issue referred to pre-menopausal patients. Although the statement did not impact on the data for the pre-menopausal patients, the statement was inaccurate and could not be substantiated. So, on these narrow grounds, the Panel ruled breaches of the Code.

5 General allegations

The complainant referred to the use of misleading and inaccurate information and the implied off-label use were not that standards that a major pharmaceutical company should hold itself to. Further the language was not responsible patient care.

The Panel noted its rulings of breaches of the Code outlined above and considered that high standards had not been maintained. It thus ruled a breach of the Code. This ruling was upheld by the Appeal Board following an appeal from Novartis.

The Panel did not consider the circumstances amounted to a breach of Clause 2 of the Code which was used as a sign of particularly censure. In this regard, it noted that it had not ruled a breach of the Code in relation to the alleged promotion which was inconsistent with the SPC. The Panel therefore ruled no breach of Clause 2 of the Code.

An anonymous individual, who described him/herself as a health professional, complained about a promotional leaflet (ref KIS19-CO25a) for Kisqali (ribociclib succinate) dated June 2019 issued by Novartis Pharmaceuticals UK Ltd. The complainant explained that he/she had attended a breast cancer conference and the leaflet was in his/her delegate bag.

Kisqali was indicated for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast

cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who had received prior endocrine therapy.

The complainant alleged that the leaflet was misleading, inaccurate and implied off-label use. The leaflet and campaign language was not responsible to patient care.

When writing to Novartis, the Authority asked it to consider the requirements of Clauses 2, 3.2, 7.2, 7.4 and 9.1 of the Code.

By way of background and to contextualise its response, Novartis explained that first-line cancer treatment was the first treatment which a patient would receive for hormone receptor positive, human epidermal growth factor receptor 2 negative (HR+, HER2-) advanced breast cancer (ABC), and second-line therapy was that which was received subsequent to this due to relapse or progression of disease. The terms first-line and second-line referred solely to the sequencing of treatment rather than to the individual classes of treatment themselves.

The 4th European School of Oncology – European Society for Medical Oncology (ESO-ESMO) International Consensus Guidelines for Advanced Breast Cancer (ABC4)[1] defined primary and secondary endocrine resistance as follows:

- Primary endocrine resistance: relapse while on the first 2 years of adjuvant endocrine therapy (ET), or progression of disease within the first 6 months of first-line ET for ABC.
- Secondary endocrine resistance: relapse while on adjuvant ET but after the first 2 years, or relapse within 12 months of completing adjuvant ET, or progression of disease after 6 months of initiating ET for ABC.

The guidelines also stated that 'ET is the preferred option for HR+ disease, even in the presence of visceral disease, unless there is visceral crisis or *concern/proof of endocrine resistance*'.

Novartis noted that Kisqali was indicated for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy (first-line), or in women who had received prior endocrine therapy (second-line).

Novartis stated that the leaflet in question discussed the use of Kisqali and ET in first-line pre-menopausal patients, focusing on overall survival (OS) data seen in this population in the MONALEESA-7 trial, which was presented at the American Society of Clinical Oncology (ASCO) congress in June 2019 (Im *et al* 2019). This was clearly stated at the outset ('What difference can first-line treatment make for premenopausal patients?'; 'First Line Kisqali – the Difference for Patients is Survival').

The leaflet was included in delegate packs at the at a breast cancer meeting, held in October 2019. Novartis, along with other pharmaceutical companies sponsored the event.

Novartis stated that MONALEESA-7 compared ribociclib or placebo in combination with endocrine therapy (goserelin plus tamoxifen or a non-steroidal aromatase inhibitor (NSAI)), in

pre/peri-menopausal patients with HR+, HER2- ABC. Patients enrolled in the trial received first-line Kisqali (or placebo) treatment in the advanced breast cancer setting. ET received in the adjuvant or neoadjuvant setting was permissible; prior ET in the advanced setting was not permitted. All patients in the intention to treat (ITT) population had only received either tamoxifen or an NSAI as a combination partner to either ribociclib or placebo as their on-study medication. The choice of endocrine partner was a stratification factor at the point of patient randomisation. No patients in this trial would have received fulvestrant as a combination partner therefore all analysis was conducted in patients having received either tamoxifen or an NSAI, with no other subgroups based on other treatment partner.

In addition to the general comments, the complainant provided further information with regard to various parts of the leaflet which were considered as follows.

1 Claim 'First-line Kisqali. The difference for patients is survival'

This was the headline claim on the leaflet which appeared below the statement 'HR+/HER2 mBC is a shattering diagnosis. What difference can first-line treatment make for premenopausal patients?'. The leaflet stated that Kisqali was the only CDK4/6 inhibitor to demonstrate significant overall survival benefit from a first-line phase III placebo-controlled trial of pre-menopausal women in combination with endocrine treatment as initial therapy.

COMPLAINT

The complainant noted that whilst Kisqali had an indication for initial endocrine-based therapy, the overall survival data referenced was only for first-line in combination with an aromatase inhibitor in endocrine-sensitive patients. There was a separate cohort of first-line advanced breast cancer patients who were endocrine resistant (ie recurred on adjuvant therapy) who would not receive aromatase inhibitor-based therapy but a fulvestrant-based therapy instead, which was not included in this data set. The complainant alleged that the claim was misleading in intent.

RESPONSE

Novartis stated that, as outlined in its background comments above, the overall survival data referenced in the leaflet referred to the MONALEESA-7 trial in which the only combination partner that would have been given was either tamoxifen or an NSAI. No patients were, nor would have been, enrolled who were treated with fulvestrant as a combination partner.

Using the ABC4 (Advanced Breast Cancer 4) guidelines outlined above, the separate cohort of first-line ABC patients referred to by the complainant who were defined as endocrine-resistant would, by the definition provided above, be those who had already been treated with endocrine therapy and relapsed, or suffered a progression of their disease. Patients in this group would then move on to second-line treatments. Therefore, the complainant's assertion that patients who relapsed on adjuvant ET and went on to be treated with fulvestrant and CDK 4/6 inhibitor (such as Kisqali) combinations would still be classed as first-line was inaccurate.

Novartis strongly denied any breach of Clause 7.2 or 7.4. The use of the term 'first-line', as explained above, was fair, accurate and balanced, and capable of substantiation.

PANEL RULING

The Panel noted the complainant's concern that there was a separate cohort of first-line advanced breast cancer patients who were endocrine resistant, ie who recurred on adjuvant therapy who would be receiving a fulvestrant-based therapy which was not included in the dataset presented in the leaflet at issue.

The Panel noted that Kisqali was indicated for advanced breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy or in women who had received prior endocrine therapy.

The Panel noted Novartis' submission that first line therapy was the first treatment which a patient would receive for hormone positive, human epidermal growth factor receptor 2 negative (HR+, HER2-) advanced breast cancer (ABC) and second-line therapy was that which was received subsequent to this due to relapse or progression of disease.

The Panel noted that the ESMO International Consensus Guidelines for advanced breast cancer definition of primary endocrine resistance included relapse while on the first 2 years of adjuvant endocrine therapy (ET) or progression of disease within the first 6 months of first-line endocrine therapy for advanced breast cancer (ABC). Secondary resistance was defined as relapse while on adjuvant ET but after the first 2 years, or relapse within 12 months of completing adjuvant ET, or progression of disease after 6 months of initiating ET for ABC.

The Panel further noted Novartis's submission that patients enrolled in the MONALEESA-7 trial received first-line Kisqali (or placebo) treatment in the advanced breast cancer setting and whilst prior endocrine therapy in the advanced breast cancer setting was not permitted, endocrine therapy received in the adjuvant or neoadjuvant setting was permissible. In the Panel's view, second-line endocrine therapy therefore related to women who had previously received endocrine therapy for advanced breast cancer and not those that had received prior endocrine therapy in the adjuvant or neoadjuvant setting.

The Panel noted that whilst the complainant referred to the cohort of patients being endocrine resistant, he/she specifically referred to the patients being first-line advanced breast cancer patients who recurred on adjuvant therapy.

In the Panel's view, first-line Kisqali, as referred to within the leaflet, could be seen as the use of Kisqali with either an aromatase inhibitor or fulvestrant as according to the Kisqali SPC each combination was indicated for initial endocrine-based therapy for the treatment of advanced breast cancer. The implication to readers might be that the overall survival data referred to within the leaflet applied to Kisqali in both combinations ie with either an aromatase inhibitor or fulvestrant which was not so.

The Panel noted that the leaflet at issue focussed on the results of a protocol-specified interim analysis of the key secondary endpoint of overall survival of the MONALEESA-7 trial data (Im *et al*). It noted Novartis' submission about the patients enrolled in the MONALEESA-7 trial. Patients received Kisqali and endocrine therapy, (goserelin plus either tamoxifen or a non-steroidal aromatase inhibitor); no patient received fulvestrant as a combination partner.

The Panel noted that there was no clear statement in the leaflet that the data related only to the first-line combination of Kisqali and an aromatase inhibitor and not fulvestrant and considered that this was misleading and, in relation to fulvestrant, was not capable of substantiation. The Panel therefore ruled a breach of Clauses 7.2 and 7.4.

2 Claim 'Kisqali is the only CDK4/6 inhibitor to demonstrate significant overall survival benefit from a first-line phase III trial in a placebo-controlled trial of premenopausal women in combination with endocrine treatment as initial therapy'.

This claim appeared in a prominent orange band across the leaflet and the second half of the claim appeared in smaller type size than the first half. Below the band was a footnote 'Kisqali is not recommended to be used in combination with tamoxifen'.

COMPLAINT

The complainant alleged that due to the explanation at Point 1 above, 'the only' was not true because another CDK4/6 inhibitor had overall survival data in first-line endocrine resistant patients (in combination with fulvestrant, rather than an aromatase inhibitor). The complainant alleged that the claim was not factually accurate.

The complainant added that 'endocrine treatment' implied either aromatase inhibitor or fulvestrant, as these were the only two endocrine treatments listed in the Kisqali marketing authorization. However, the study did not include the fulvestrant combination, and instead included aromatase inhibitor or tamoxifen. The tamoxifen combination was not within Kisqali's marketing authorization. The complainant alleged that the claim was misleading and promoted off-licence use.

RESPONSE

Novartis noted the allegation that the claim was inaccurate but stated, as described above, endocrine-resistant patients who went on to be treated with CDK4/6 inhibitor and fulvestrant combinations would not be classed as first-line patients. Rather, they would be considered second-line.

Novartis stated that the other CDK4/6 inhibitor with statistically significant overall survival data referred to by the complainant, was abemaciclib. The data referred to was from the MONARCH-2 (Sledge *et al* 2019) study of abemaciclib in combination with fulvestrant after initial endocrine therapy on which patients had progressed, ie a second-line population rather than a first-line population as the complainant claimed.

The other references in the leaflet following the claim in question referred to trials of the other CDK4/6 inhibitors currently available on the market. Of these, the trials in which overall survival data was available showed this data to be either non-significant, or demonstrated when used second-line.

Therefore, consistent with the summary of product characteristics (SPC) and the ABC4 definition of endocrine resistance, as well as demonstrating that none of the other CDK4/6 inhibitors currently available had yet demonstrated statistically significant overall survival data in a first-line setting (as shown in the MONALEESA-7 trial), Novartis strongly submitted that the claim was adequately substantiated and appropriate.

The claim (in its entirety) that 'Kisqali is the only CDK4/6 inhibitor to demonstrate a significant OS benefit from a first-line phase III trial, in a placebo-controlled trial of premenopausal women in combination with endocrine treatment as initial therapy' was not inaccurate and could be

substantiated. Novartis maintained that, in the context of Clauses 7.2 and 7.4, it had acted in accordance with the letter and spirit of the Code.

With regard to the allegation that initial ET also included tamoxifen, which Kisqali was not recommended for use in combination with, and that Novartis had therefore promoted off-licence use; Novartis noted that the leaflet included a prominent statement that 'Kisqali is not recommended for use with tamoxifen'. This statement was also included in the prescribing information. To avoid any misinterpretation, Novartis chose to use the wording from Sections 4.4 and 4.5 of the Kisqali SPC, 'Kisqali is not recommended to be used in combination with tamoxifen'.

Novartis denied any breach of Clause 3.2 as the leaflet clearly stated that Kisqali was not recommended for use in combination with tamoxifen, consistent with the wording in its SPC.

Novartis also denied any breaches of Clauses 7.2 or 7.4 of the Code; the information and claims referenced in this complaint were fair, accurate, balanced, not misleading and capable of substantiation.

PANEL RULING

The Panel noted that the complainant did not identify the other CDK4/6 inhibitor or the study to which he/she referred to with regard to overall survival data in combination with fulvestrant. Novartis identified the CDK4/6 inhibitor with statistically significant overall survival data, as abemaciclib and the study as MONARCH 2 (Sledge *et al* 2019).

The Panel noted that like Kisqali, abemaciclib (Verzenios) was indicated for the treatment of women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who had received prior endocrine therapy.

The Panel noted that MONARCH 2 (Sledge *et al* 2019) was a double-blind, placebo-controlled phase III study of abemaciclib plus fulvestrant vs placebo plus fulvestrant in women with HR-positive, ERBB2 (formerly HER2)-negative advanced breast cancer who progressed during prior endocrine therapy. This included women who progressed during neoadjuvant or adjuvant endocrine therapy, within 12 months after adjuvant endocrine therapy, or whilst receiving first-line endocrine therapy for advanced breast cancer. The latter did not appear to be the subject of a subgroup analysis.

The Panel noted Novartis' submission with regard to the definition of primary and secondary endocrine resistance and what was meant by first-line and second-line treatment and that the MONARCH 2 population was a second-line population. It appeared to the Panel, however, that patients studied in MONARCH 2 were a mixture of first-line and second-line population in relation to advanced breast cancer. Outcome survival data for the first line patients did not appear to have been reported separately. MONARCH 2 was on pre-, peri- and post-menopausal women and again the first-line population data for pre- and peri-menopausal patients did not appear to have been reported separately.

The Panel did not consider that the complainant had provided evidence to show that the claim that Kisqali was the only CDK4/6 inhibitor to demonstrate significant overall survival benefit from

a first-line phase III trial in a placebo-controlled trial of pre-menopausal women in combination with endocrine treatment as initial therapy was misleading or incapable of substantiation. The Panel therefore ruled no breach of Clauses 7.2 and 7.4.

The Panel noted that the Kisqali SPC referred to its use in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy. In the Panel's view, as noted above, endocrine treatment, as referred to within the leaflet, could be seen as the use of Kisqali with either an aromatase inhibitor or fulvestrant.

The Panel noted that the leaflet at issue focussed on the results of a protocol-specified interim analysis of the key secondary endpoint of overall survival of the MONALEESA-7 trial data (Im *et al*). It noted Novartis' submission that patients enrolled in the MONALEESA-7 trial received Kisqali and endocrine therapy, (goserelin plus either tamoxifen or a non-steroidal aromatase inhibitor). The Panel noted that subgroup analyses, according to endocrine therapy, were prespecified to be performed if the results of the analysis of overall survival in the intention to treat population were significant. This further evaluation of the MONALEESA-7 trial data was carried out according to whether patients received an aromatase inhibitor or tamoxifen as the combination partner with Kisqali or placebo.

The Panel noted that there was no clear statement in the leaflet that the claims referred to were only in relation to Kisqali in combination with an aromatase inhibitor and not in combination with tamoxifen. In the Panel's view, there was, therefore, an implication that the data also referred to the combination with tamoxifen which was misleading and a breach of Clause 7.2 was ruled.

Section 4.4 of the Kisqali SPC referred to QT interval prolongation results from MONALEESA-7 and included the statement that 'Kisqali is not recommended to be used in combination with tamoxifen (see sections 4.8 and 5.1'. There was a similar reference in Section 4.5. This meant that some of the data in MONALEESA-7 would not be in line with the Kisqali summary of product characteristics. The SPC included details about MONALEESA-7 and its results in Section 5.1.

The Panel noted that there was a difference between using data from a study, which included licensed and unlicensed doses to substantiate a specific, within licence claim, and general use for promotional purposes of a study that used licensed and unlicensed doses. The Panel did not consider that the reference to the overall MONALEESA-7 data which included the use of a combination that was inconsistent with the particulars listed in the Kisqali SPC necessarily meant that there had been a breach of Clause 3.2. The data referred to in the leaflet was that covered by the indication for Kisqali. There were no specific claims for the results with tamoxifen and the leaflet clearly stated that Kisqali was not recommended to be used in combination with tamoxifen. Whilst noting its ruling above regarding Clause 7.2 and that the leaflet could have been clearer that the claims within it were only in relation to Kisqali in combination with an aromatase inhibitor, the Panel did not consider that, taking all the circumstances into account, the leaflet was inconsistent with the SPC and thus ruled no breach of Clause 3.2.

3 Claim 'Kisqali is not recommended to be used in combination with tamoxifen'

COMPLAINT

The complainant noted that generally in the UK, 'recommended' was used to imply reimbursement (as the National Institute for health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC) used 'recommended' in technology appraisal documents to indicate a positive statement). The complainant noted, however, that not only did Kisqali not have reimbursement for use with tamoxifen, it did not have a marketing authorization to be used with tamoxifen. The complainant alleged that the claim was misleading and promoted off-licence use.

RESPONSE

Novartis disagreed that 'recommend' referred only to indicate positive statements by NICE. Within the context of a pharmaceutical leaflet the word referred to the wording used within the prescribing information and SPC for products to denote circumstances in which a product should or should not be used.

In this instance, and as already stated above, the leaflet very clearly stated on the first page that 'Kisqali is not recommended for use with tamoxifen', as it did on the prescribing information overleaf. That wording was taken directly from the SPC. To claim that the statement was inappropriate in the context of the existing NICE guidelines for Kisqali, as well as claiming that Novartis had promoted off-licence, was a misinterpretation of the context and intent of the statement.

Novartis denied a breach of Clause 3.2.

PANEL RULING

The Panel considered that the important point was that Kisqail was not recommended to be used with Tamoxifen. It did not consider that the audience would interpret this statement in relation to reimbursement. The Panel did not consider that the statement, in itself, meant that the leaflet promoted Kisqali in a manner that was inconsistent with the SPC. No breach of Clause 3.2 of the Code was ruled based on the narrow allegation.

4 Statement '[Overall survival] Data from MONALEESA – 2 and MONALEESA – 3 phase III trials in postmenopausal women with HR+/HER2 – advanced breast cancer are not available yet'

This statement appeared as a footnote to the claim considered at Point 2 above.

COMPLAINT

The complainant noted that the leaflet was disseminated at the meeting on 4 October 2019, five days after overall survival data for MONALEESA-3 was released at ESMO, as was overall survival data for abemaciclib in the same session, so the statement at issue was not accurate. The complainant acknowledged that it would take Novartis time to turn around a new document, but as the company knew in July that the data would be released at ESMO, it should not have sent an outdated and inaccurate leaflet to the meeting on 4 October – it should have been withdrawn.

RESPONSE

Novartis stated that when the leaflet was developed and certified, the overall survival data from MONALEESA-3 was not publicly available. However, the MONALEESA-3 OS data was presented at ESMO, a few days before the meeting at which the complainant received the leaflet.

Despite this, Novartis submitted that the item was still appropriate for use at the meeting. As previously mentioned, the leaflet was solely about MONALEESA-7 and the overall survival data observed within that trial and its pre-menopausal population alone. The leaflet did not include any claims about the efficacy of Kisqali in the post-menopausal populations enrolled in MONALEESA-2 and -3. Upon reflection, the statement at issue was perhaps unnecessary.

Furthermore, although the overall survival data from the MONALEESA-3 study in a post-menopausal population was presented at the 2019 ESMO congress, along with data from the MONARCH-2 trial of abemaciclib and fulvestrant after initial endocrine therapy, none of the data from either of those studies invalidated the claims in the leaflet at issue about the overall survival data from MONALEESA-7. Therefore, the data within the leaflet was valid, accurate, and capable of substantiation regardless of any data from MONALEESA-2, MONALEESA-3, and MONARCH-2.

Novartis noted that commercial staff present at the meeting had been fully trained on the MONALEESA-3 data (training sessions were held on 2 and 3 October 2019).

Novartis denied a breach of Clauses 7.2 and 7.4.

PANEL RULING

The Panel considered that, at the time the leaflet was used, it was not true to state that the overall survival data from MONSLESSA-3 were not available. These were in the public domain prior to the meeting at which the leaflet was used. This data related to post-menopausal patients whereas the leaflet at issue referred to pre-menopausal patients. Although the statement did not impact on the data for the pre-menopausal patients, the statement was inaccurate and could not be substantiated. So, on these narrow grounds, the Panel ruled breaches of Clauses 7.2 and 7.4 of the Code.

5 General allegations

COMPLAINT

The complainant referred to the use of misleading and inaccurate information and the implied off-label use were not that standards that a major pharmaceutical company should hold itself to. Further the language was not responsible patient care.

RESPONSE

Novartis stated that a final medical signatory certified the leaflet as being fair, accurate, balanced, and capable of substantiation in accordance with Clauses 7.2 and 7.4. All of the information contained was on-licence, in accordance with Clause 3.2, and Novartis therefore rejected any assertion that high standards were not maintained and that continued use of the item represented bringing discredit to, and reducing confidence in, the industry. As such, it had acted in accordance with Clauses 2 and 9.1 of the Code.

PANEL RULING

The Panel noted its rulings of breaches of the Code outlined above and considered that high standards had not been maintained. It thus ruled a breach of Clause 9.1 of the Code. This ruling was appealed.

The Panel did not consider the circumstances amounted to a breach of Clause 2 of the Code which was used as a sign of particularly censure. In this regard, it noted that it had not ruled a breach of the Code in relation to the alleged promotion which was inconsistent with the SPC. The Panel therefore ruled no breach of Clause 2 of the Code.

APPEAL BY NOVARTIS

Novartis submitted that the breaches of Clauses 7.2 and 7.4 did not constitute a failure to maintain high standards. These breaches were not a deliberate attempt to mislead the audience of the item; were not a result of systemic company failings; and did not result in any risk to patient safety. The intent of the item and the claims within it were appropriate and capable of substantiation within the spirit of the Code, the breaches of Clauses 7.2 and 7.4 were ruled due to a lack of complete clarity within the leaflet.

Novartis noted its reasoning, in the context of the relevant Panel rulings below:

> 'The Panel noted that there was no clear statement in the leaflet that the data related only to the first-line combination of Kisqali and an aromatase inhibitor and not fulvestrant and considered that this was misleading and in relation to fulvestrant was not capable of substantiation. The Panel therefore ruled a breach of Clauses 7.2 and 7.4.'

Novartis submitted that its use of the term 'first-line' was congruent with the terminology used by NICE regarding CDK4/6 inhibitor combination treatments. As per NICE criteria, CDK4/6 inhibitors in combination with aromatase inhibitors were recommended as initial therapy ('first-line', where a patient had not received prior endocrine therapy), and CDK4/6 inhibitors in combination with fulvestrant were reimbursed only where patients had progressed following initial endocrine therapy (or had progressed up to 12 months after (neo)adjuvant endocrine therapy, 'second-line').

Novartis submitted that considering that NICE guidance provided the eligibility for reimbursed treatment of NHS patients, it would be considered reasonable that reference to 'first-line' would lead UK oncology health professionals (the target audience) to conclude that the item was referring to Kisqali in combination with an aromatase inhibitor. At all times it was Novartis' intention to maintain high standards with no intention to deliberately mislead or make claims that were incapable of substantiation. However, to avoid any risk of ambiguity, Novartis agreed to make future materials even more explicitly clear when discussing treatment combinations with Kisqali in relation to the MONALEESA-7 study.

> 'The Panel noted that there was no clear statement in the leaflet that the claims referred to were only in relation to Kisqali in combination with an aromatase inhibitor and not in combination with tamoxifen. In the Panel's view there was therefore an implication that the data also referred to the combination with tamoxifen which was misleading and a breach of Clause 7.2 was ruled.'

Novartis submitted that it had included a prominent statement in the leaflet that 'Kisqali was not recommended in combination with tamoxifen' as per Kisqali's marketing authorisation. The inclusion of this statement was with the specific intent of ensuring the audience understood that the claims being made were in relation to Kisqali in combination with an aromatase inhibitor. In its ruling, the Panel acknowledged that it 'did not consider that, taking all the circumstances into account, the leaflet was inconsistent with the SPC' and not in breach of Clause 3.2, thereby acknowledging that there was not a deliberate attempt to mislead. In this context, it seemed unreasonable that this should contribute to the ruling of a failure to maintain high standards.

> 'The Panel considered that at the time the leaflet was used it was not true to state that the overall survival data from MONSLESSA-3 [sic] were not available. These were in the public domain prior to the meeting at which the leaflet was used. This data related to postmenopausal patients whereas the leaflet at issue referred to premenopausal patients.
>
> Although the statement did not impact on the data for the premenopausal patients, the statement was inaccurate and could not be substantiated. So on these narrow grounds the Panel ruled breaches of Clauses 7.2 and 7.4 of the Code.'

Novartis submitted that it was not the intention to mislead the audience or gain an inappropriate advantage by including the above statement. The intention was to highlight to the audience that there was ongoing evidence generation within the relevant therapeutic area. The Panel noted that this statement did not impact upon the data or claims presented in the item itself, as MONALEESA-3 was a trial of post-menopausal patients. The presence of this statement, while not up-to-date at the time of this particular case, did not contradict the claims in the leaflet and thus did not mislead the reader with regard to the safe use of Kisqali. As such, while the statement should have been removed upon the release of Novartis' MONALEESA-3 data, it remaining on the item was not due to any inappropriate intent or systematic failure. Novartis submitted that it was committed to ensuring that future materials with such statements were withdrawn and/or updated when they no longer applied.

Novartis submitted that it would like to take the opportunity to reassure the Panel that Novartis had learnt from the Panel's perspective on ambiguity arising from this case. In particular, with regard to MONALEESA-7, the study relevant to this case, Novartis had committed to being even more specific when describing combination treatments to minimise the potential risks of ambiguity.

Novartis submitted that it would also like the Appeal Board to consider the implications of this case. The breaches of Clauses 7.2 and 7.4 occurred without any intent to mislead and there had been no risk to patients. If these breaches were deemed to result in a breach of Clause 9.1, this decision should be consistent with Panel rulings for other similar cases and should be supportive of the spirit of learning from self-regulation.

In that regard, Novartis referred to Case AUTH/2923/12/16 and Case AUTH/2953/4/17, with the latter case having been heard by the Appeal Board. In both cases, claims were found to be exaggerated and misleading, and while found in breach of Clauses 7.2 and/or 7.4 of the Code, neither were deemed to amount to a failure to maintain high standards and no breach of Clause 9.1 of the Code was ruled.

Novartis submitted that it took its obligations with regards to compliance with the Code very seriously. Novartis' commitments of undertaking and assurance, in accordance with Paragraph 7.1 of the Constitution and Procedure for the PMCPA, had been considered of the utmost importance.

COMMENTS FROM THE COMPLAINANT

There were no comments from the complainant.

APPEAL BOARD RULING

The Appeal Board noted that Novartis accepted the rulings of the Panel other than the ruling of a breach of Clause 9.1 at Point 5 above. In ruling the breach of Clause 9.1, the Panel had referred to its rulings of breaches of the Code (Points 1, 2 and 4).

The Appeal Board noted that Novartis referred to two previously published cases (Case AUTH/2923/12/16 and Case AUTH/2953/4/17) in support of its appeal, in which there had been rulings of breaches of Clauses 7.2 and/or 7.4 and no breach of Clause 9.1. The Appeal Board noted that there were differences between these cases and the appeal and queried whether the cases cited were directly applicable. The Appeal Board noted that there were far more cases in which a breach of both Clauses 7 and 9.1 had been ruled. In any event, each case was considered on its individual merits based on the evidence provided.

The Appeal Board noted that the leaflet at issue focussed on the results of a protocol-specified interim analysis of the key secondary endpoint of overall survival of the MONALEESA-7 trial data (Im *et al*). On the front page of the leaflet the statement '[Overall survival] Data from MONALEESA – 2 and MONALEESA – 3 phase III trials in postmenopausal women with HR+/HER2 – advanced breast cancer are not available yet' appeared as a footnote to the claim considered at Point 2 above. The Appeal Board noted that the leaflet, dated June 2019, was disseminated at a meeting on 4 October 2019, five days after overall survival data for MONALEESA-3 was released at ESMO. The Appeal Board noted from the company representatives at the appeal that the company (in particular global) would have known about the new data some time before the meeting at issue, but the representatives were unable to confirm when this was. The Novartis representatives said that they would have been aware of the data about a month before the meeting at which the leaflet in question was used. The Appeal Board noted that the complainant stated that Novartis would have known in July that the data were to be released at ESMO. The Appeal Board noted that none of the representatives from Novartis at the appeal knew that the leaflet at issue had been used at the meeting on 4 October 2019 until the complaint was received from the PMCPA. The Appeal Board considered that the leaflet in question should not have been used at the meeting on 4 October as it should have been withdrawn and/or amended. In this regard the Appeal Board noted the company representatives accepted that the material should have been withdrawn as soon as the data was published.

The Appeal Board noted Novartis' submission that the audience would understand that the reference to first line in the leaflet was in relation to the NICE guidance which provided the eligibility for reimbursed treatment of NHS patients. The Appeal Board did not consider that reference to 'first-line' would lead UK oncology health professionals (the target audience) to conclude the item was referring only to Kisqali in combination with an aromatase inhibitor as, according to Novartis's submission, CDK4/6 inhibitors in combination with fulvestrant were

reimbursed only where patients had progressed following initial endocrine therapy (or had progressed up to 12 months after (neo)adjuvant endocrine therapy, 'second-line'). Kisqali was indicated for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who had received prior endocrine therapy.

The Appeal Board noted the company's appeal and its representatives at the appeal stated that the company had not intended to mislead and considered that the company's lack of intent was not relevant to whether it had breached Clause 9.1 of the Code. Nor did it accept Novartis' submission that the Panel's ruling of no breach of Clause 3.2 meant that there had not been a failure to maintain high standards.

The Appeal Board noted its comments above and that the Panel had made five rulings of breaches of the Code, including that the leaflet was inaccurate and misleading with regard to the use of Kisqali. Further Novartis had failed to remove/amend the leaflet in light of new data. The Appeal Board was concerned about what it considered to be Novartis' poor governance and apparent lack of care in this regard. Consequently, the Appeal Board considered that Novartis had failed to maintain high standards and it upheld the Panel's ruling of a breach of Clause 9.1. The appeal was unsuccessful.

Complaint received **3 October 2019**

Case completed **4 August 2020**