CASE AUTH/3665/6/22

ANONYMOUS HEALTH PROFESSIONAL v NOVARTIS

Concerns about misleading claims about Entresto on a Novartis website

CASE SUMMARY

This case was in relation to the promotion of Entresto on a Novartis website.

The Panel ruled a breach of the following Clauses of the 2021 Code in relation to the claim 'National guidelines support ENTRESTO as a 1st line treatment option in chronic HFrEF' not being sufficiently complete, as in the Panel's view, the broad target audience, which included 'Physician; Pharmacist; Payor / Health Insurance / Nurse / Other Healthcare Stakeholder' according to the certificate, was unlikely to all be aware that the definition of HFrEF was less than 40% LVEF:

Breach of Clause 6.1	**Requirement that material must be sufficiently complete to enable recipients to form their own opinion of the therapeutic value of the medicine**
Breach of Clause 5.1	**Failure to maintain high standards**

The Panel ruled no breach of the following Clauses of the 2021 Code in relation to the claim 'National guidelines support ENTRESTO as a 1st line treatment option in chronic HFrEF' as the complainant had not provided reasons or evidence and thereby established that the claim was incapable of substantiation, and because Clause 2 was a sign of particular censure which was not warranted in the particular circumstances of this case:

No Breach of Clause 6.2	**Requirement that claims must be capable of substantiation**
No Breach of Clause 2	**Requirement that activities or material must not bring discredit upon, or reduce confidence in, the pharmaceutical industry**

The Panel ruled no breach of the following Clause of the 2021 Code in relation to the claim 'Starting ENTRESTO can lead to substantial improvements in social and physical activities comparable to feeling 9 YEARS YOUNGER vs ACEi (enalapril)*' as the Panel did not consider that the use of the asterisk which stated that the claim was based on a secondary analysis of a study meant that the claim in question hid that it was not based on primary endpoint data:

No breach of Clause 6.1	**Requirement that claims must not be misleading**

The Panel ruled no breach of the following Clauses of the 2021 Code for each of the following claims: 'Improve the chronic HFrEF patient's experience vs ACEi (enalapril) - improvements in quality of life', 'Patients on ENTRESTO feel better, stay out of the

hospital, and live longer vs ACEi (enalapril)', 'Starting ENTRESTO can lead to substantial improvements in social and physical activities comparable to feeling 9 YEARS YOUNGER vs ACEi (enalapril)*'(Clause 6.1 covered above), as in relation to each allegation the complainant was unable to establish their case:

No Breach of Clause 6.1	**Requirement that claims must not be misleading**
No Breach of Clause 6.2	**Requirement that claims must be capable of substantiation**
No Breach of Clause 5.1	**Requirement to maintain high standards**
No Breach of Clause 2	**Requirement that activities or material must not bring discredit upon, or reduce confidence in, the pharmaceutical industry**

This summary is not intended to be read in isolation.
For full details, please see the full case report below.

FULL CASE REPORT

A complaint was received from an anonymous, contactable complainant who described themselves as a health professional about claims on a Novartis website about Entresto. (sacubitril/valsartan).

COMPLAINT

The complainant alleged that misleading claims were portrayed around usage of Entresto on the following webpage: https://www.health.novartis.co.uk/medicines/cardio-metabolic/entresto UK | October 2021 |145880.

(1) https://www.health.novartis.co.uk/medicines/cardio-metabolic/entresto. The complainant stated that on this page, a variety of claims were provided around Entresto. One of these was 'Improve the chronic HFrEF patient's experience vs ACEi (enalapril) - improvements in quality of life'. This was a misleading and unqualified claim, according to the complainant, as the exact patient experience benefits were not provided either adjacent to the claim or directly below. 'Patient experience' was very broad and could mean a number of clinical outputs in cardiology space. Furthermore, improved quality of life was not seen as a primary endpoint of Entresto vs Enalapril trials. The complainant stated that quality of life outcomes were only part of a secondary analysis and post-hoc analysis and not a primary endpoint. This was not made clear anywhere on this claim and the primary endpoints were not given. Code breaches of Clauses 6.1, 6.2, 5.1 and 2 were alleged.

(2) The complainant further highlighted another claim on the same page(https://www.health.novartis.co.uk/medicines/cardio-metabolic/entresto) mentioned 'National guidelines support ENTRESTO as a 1st line treatment option in chronic HFrEF1'. The complainant stated this claim was inaccurate and misleading as Entresto was recommended as RAASi of choice when LVEF was <40%by Heart Failure Hub Scotland guidelines. This sentence had not been qualified under the claim, according to the complainant, as this was a very specific recommendation especially around lowered ejection fraction threshold of less than 40. Code breaches of Clauses 6.1, 6.2, 5.1 and 2 were alleged.

(3)https://www.health.novartis.co.uk/medicines/cardio-metabolic/entresto/chronic-HFrEF-disease-trajectory UK | October 2021 | 145888. The complainant stated at the top of this page, Novartis had the following claim 'Patients on ENTRESTO feel better, stay out of the hospital, and live longer vs ACEi (enalapril)1–7'. This claim was not all primary endpoint data, post-hoc analysis had taken place for some clinical outcomes mentioned in this claim but Novartis had not made this clear. The complainant alleged this was misleading as there was a significant difference of primary endpoint in a clinical trial vs doing a post-hoc analysis. Code breaches of Clauses 6.1, 6.2, 5.1 and 2 were alleged.

(4)https://www.health.novartis.co.uk/medicines/cardio-metabolic/entresto/improvements-in-quality-of-life UK | October 2021 | 145891. The complainant stated this page was dedicated to improvements in quality of life. One of the key claims on this page was 'Starting ENTRESTO can lead to substantial improvements in social and physical activities comparable to feeling 9 YEARS YOUNGER vs ACEi (enalapril):*1'. This claim was only a secondary analysis and not a primary endpoint. The complainant alleged the use of a * at the end of this claim demonstrated how Novartis were concerned about making clear and prominent that this was not a primary endpoint and essentially hiding this important information. Code breaches of Clauses 6.1, 6.2, 5.1 and 2 were alleged.

The complainant stated as a health professional, it was disappointing that such claims across the content had been made around clinical outcomes which were not based on primary endpoint data. Furthermore, if the claims were to be used it should have been made clear in prominence that these were all only secondary data analysis or post-hoc analysis and not a primary endpoint outcome.

When writing to Novartis, the Authority asked it to consider the requirements of Clauses 2, 5.1, 6.1 and 6.2 of the 2021 Code as cited by the complainant.

RESPONSE

Novartis stated that the complaint caused it concern and it had taken its content seriously. Novartis was committed to operating in accordance with the required standards and meeting the relevant requirements and expectations.

1. Background

Novartis submitted the Complaint related to three webpages on the health.novartis.co.uk website (the "**Website**") which hosted promotional information about Novartis products aimed at UK healthcare professionals. Each time a healthcare professional accessed the Website they were asked to confirm that they were a healthcare professional (or NHS relevant decision-maker). The Website hosted a dedicated section on Entresto. This section contained prescribing information, licensed indications, safety and efficacy data and other resources to support health professionals ("**HCPs**") prescribing Entresto.

According to Novartis, the webpages were live at the time of the complaint and provided publication dates.

2. Novartis Response

Novartis submitted claims 1 to 4 below were fully supported by the pivotal double blind Novartis PARADIGM-HF trial[1]. During this trial, 8442 New York Heart Association ("**NYHA**") class II – IV HFrEF patients received either Entresto (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily). The relevant primary, secondary and exploratory endpoints were listed by Novartis as follows:

- *Primary endpoint*
    - The primary endpoint was a composite of death from cardiovascular causes or hospitalisation for heart failure.

- *Secondary endpoint(s)*
    - The secondary endpoints included:
        - the time to death from any cause, and
        - the change from baseline to 8 months in the clinical summary score on the Kansas City Cardiomyopathy Questionnaire ("**KCCQ**") (on a scale from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure).

- *Exploratory endpoint*
    - The exploratory endpoint was to compare the effects of Entresto and Enalapril on improving health-related quality of life (assessed by total score and individual scores of the sub-domains from the KCCQ and the total score of the EuroQol [EQ-5D] for health status).

- Novartis submitted endpoints were assessed using a sequentially rejective procedure with the first two secondary end points at the highest level of the testing sequence (including overall QoL assessed by the effect on KCCQ clinical summary score). The study demonstrated superiority of Entresto vs enalapril on all of these pre-specified endpoints. The trial was stopped early, according to prespecified rules, after a median follow-up of 27 months, because the boundary for an overwhelming benefit with Entresto had been crossed. Novartis submitted at the time of study closure, the primary endpoint had occurred in 914 patients (21.8%) in the Entresto group and 1117 patients (26.5%) in the enalapril group (hazard ratio in the Entresto group, 0.80; 95% confidence interval [CI], 0.73 to 0.87; P<0.001).

- Novartis stated a total of 711 patients (17.0%) receiving Entresto and 835 patients (19.8%) receiving enalapril died (hazard ratio for death from any cause, 0.84; 95% CI, 0.76 to 0.93; P<0.001); of these patients, 558 (13.3%) and 693 (16.5%), respectively, died from cardiovascular causes (hazard ratio, 0.80; 95% CI, 0.71 to 0.89; P<0.001). As compared with enalapril, Entresto also reduced the risk of hospitalization for heart failure by 21% (P<0.001) and decreased the symptoms and physical limitations of heart failure (P = 0.001).

- According to Novartis, this PARADIGM-HF trial was the largest pharmacological trial conducted in patients with heart failure and reduced ejection fraction. In this trial, Entresto was superior to enalapril in reducing the risks of death and of hospitalization for heart failure and this formed the basis for Claims 1 to 4. All of the claims were hence supported by not only the primary and secondary endpoints, but also the post-hoc analysis which

further confirmed the primary and secondary findings and were hence not misleading to use.

Responses were given by Novartis for the specific complaints as grouped in Table 1:

(A) Entresto (sacubitril/valsartan) webpage

Claim 1
"Improve the chronic HFrEF patient's experience vs ACEi (enalapril) - improvements in quality of life."

- Entresto demonstrated superiority vs enalapril on all pre-specified endpoints, which included reducing hospitalisations, and improving symptoms and physical activity on the KCCQ as a secondary endpoint.

- Claim 1 is neither misleading, nor unqualified, as alleged by the complainant. This claim was positioned on the Entresto product homepage. As a homepage, this webpage naturally lead to further pages that provided additional information. The "*Improvements in quality of life*" phrase of Claim 1 was a tab. Clicking on this tab lead the user to a webpage, which explained the substantial improvements in social and physical activities that Entresto could lead to compared to ACEi (enalapril) (see Enclosure 3 for a copy of this webpage). From the positioning of the 'improvements in quality of life' tab on the Entresto homepage, it was very clear to a user at the outset that, once clicked on, this tab would lead the user to further information. The follow-on page showed that 'patient experience', as referenced in Claim 1, covered a range of measures including improvements in sexual relationships, hobbies and recreation, household chores, gardening, and how patients felt compared to ACEi (enalapril). Therefore, this was neither misleading nor unqualified as alleged by the complainant.

Improvement in quality of life was a claim further supported by two studies explained below, namely Chandra et al (2018) and Lewis et al. (2017):

- Chandra et al (2018) was a post hoc secondary analysis of the PARADIGM-HF trial described above. Patients completed Health Related Quality of Life ("**HRQL**") assessments using the KCCQ at randomization, 4-month, 8-month, and annual visits. The effect of Entresto on components of the physical and social limitation sections of the KCCQ at 8 months and longitudinally, related biomarkers and clinical outcomes were studied. The KCCQ was a widely used, 23-item, self-administered, disease specific HRQL instrument that had been validated for heart failure. It was initially administered during the randomization visit, which served as baseline. It was administered again at 4, 8, 12, 24, and 36 months or until the final visit. The principal HRQL efficacy time point was prespecified at 8 months.

- At baseline, 7618 of 8399 (90.7%) patients completed the initial KCCQ assessment. Patients receiving Entresto had significantly better adjusted change scores in most physical and social activities at 8 months and for 36 months compared with those receiving enalapril. The largest improvement over enalapril was in household chores (adjusted change score difference, 2.35; 95%CI, 1.19-3.50; P < .001) and sexual relationships (adjusted change score difference, 2.72; 95%CI, 0.97-4.46; P = .002); both persisted through 36 months (overall change score difference, 1.69 [95%CI, 0.78-2.60], P < .001;

and 2.36 [95%CI, 1.01-3.71], P = .001, respectively). This data substantiated the claim of improved QoL vs an ACEi. Specifically, 7 out of 10 physical and social activities were significantly improved vs the enalapril group, including elements such as the "ability to do chores".

- The Lewis et al. 2017 study reported the primary quality of life endpoints from the PARADIGM-HF trial. Among the 8399 patients enrolled in PARADIGM-HF, 7623 (91%) completed KCCQ scores at randomisation with complete data at 8 months for 6881 patients (90% of baseline). At 8 months, Entresto group noted improvements in both KCCQ clinical summary score (+0.64 versus −0.29; P=0.008) and KCCQ overall summary score (+1.13 versus −0.14; P<0.001) in comparison to enalapril group and significantly less proportion of patients with deterioration (≥5 points decrease) of both KCCQ scores (27% versus 31%; P=0.01). Adjusted change scores demonstrated consistent improvements in Entresto compared with enalapril through 36 months. There was a consistent effect of sacubitril/valsartan across all 8 quality of life domains. These findings demonstrated that Entresto lead to better HRQL in surviving patients with heart failure. This data also substantiated the claim.

- These endpoints are supportive of the primary and secondary endpoints of the PARADIGM study, which was a composite of CV death or first HF hospitalisation. As stated above, the primary endpoint was met and Entresto was superior to enalapril in reducing the risks of death and of hospitalisation for heart failure. Novartis made no attempt to conceal this information as:

    - The footnotes to Claim 1 on the Entresto homepage explained the study designs of the Chandra publication and the Lewis publication.

    - The first footnote on the webpage dedicated to the improvements in quality of life stated the primary endpoint of the PARADIGM-HF trial clearly.

    - Claims on the webpage dedicated to the improvements in quality of life state in the footnotes that they are based on a post-hoc analysis of the PARADIGM-HF trial where applicable. These claims were also supported by the secondary endpoint from the PARADIGM-HF trial. This endpoint focused on the change from baseline to 8 months in the KCCQ. This endpoint was met, further supporting the QoL claims.

- Claim 1 was an accurate, balanced, unambiguous claim, which was capable of substantiation. Claim 1 was not misleading or unqualified. Therefore, there has been no breach of Clauses 6.1, 6.2, 5.1 or 2 of the Code on this point.

Claim 2

"*National guidelines support ENTRESTO as a 1st line treatment option in chronic HFrEF*".

The statement from the Heart failure Hub Scotland Guidelines referred to by the Complainant stated: *"Select, where possible and where appropriate, therapies that require the fewest titration steps eg. Bisoprolol as BB of choice and Sacubitril Valsartan as RAASi of choice when left ventricular ejection fraction (EF) is less than 40%."*

- The universal definition of Heart failure with Reduced Ejection Fraction (HFrEF) was HF with an ejection fraction of <40%. In the UK NICE guideline[9], within the definition of terms, it was clearly stated that Heart failure with reduced ejection fraction was Heart failure with an ejection fraction below 40%. This was consistent across other UK, European and American Guidelines[8-12]. Therefore, stating HFrEF within the claim meant a HF with an ejection fraction of <40%, and no further clarification was necessary.

- Claim 2 stated, *"…1st line treatment option in chronic HFrEF".* Given that there was no other definition of HFrEF available, it was not necessary to further explain that the ejection fraction being referred to here was <40%. The audience of this website were healthcare professionals or NHS relevant decision-makers, who one could expect would understand the meaning of HFrEF, so further qualification, definition or explanation was not necessary. Use of the word "*option*" in Claim 2 highlighted to the reader that other medicine options remained available.

- Claim 2 was not inaccurate, misleading or unqualified. Therefore, there had been no breach of Clauses 6.1, 6.2, 5.1 or 2 of the Code on this point.

(B) Chronic HFrEF Disease Trajectory webpage

Claim 3
"*Patients on ENTRESTO feel better, stay out of the hospital, and live longer vs ACEi (enalapril)".*

This claim was fully substantiated by the pivotal PARADIGM trial as explained above, as well as other references for the reasons set out below:

- "*Patients on ENTRESTO feel better*" – this section of the claim referred to quality of life and was also supported by formal QoL assessment in the PARADIGM-HF trial, as highlighted in Section A above.

- *"stay out of the hospital, and live longer vs ACEi (enalapril)"* – this referred to a reduction in mortality and hospitalisation seen in the PARADIGM study as explained above. This data supported this aspect of the claim fully and since the primary endpoint was met, stating the information in the footnote was not an attempt by Novartis to 'hide' this information.

- The entirety of this claim was fully supported by the PARADIGM-HF trial. Specifically, the trial demonstrated that Entresto was superior to enalapril in reducing the risks of death and of hospitalisation for heart failure. The trial also showed that as compared with enalapril, Entresto also decreased the symptoms and physical limitations of heart failure (P = 0.001). The primary endpoint in the study was a composite of death from cardiovascular causes or hospitalization for heart failure whilst one of the secondary endpoints was the change from baseline to 8 months in the clinical summary score on KCCQ (a QoL measure). Therefore, this claim was based on a combination of endpoints. Both of these endpoints were met so a claim that combines both endpoints would not be unacceptable under the Code.

- The post-hoc or secondary analysis were supportive to the findings in the PARADIGM-HF trial (where primary and secondary endpoints were met demonstrating superiority in reduced hospitalisations and improved symptoms and physical activity on the KCCQ), hence use of these analyses were not misleading.

- Claim 3 was an accurate, balanced, unambiguous claim, which was capable of substantiation. Claim 3 was not misleading or unqualified. Therefore, there had been no breach of Clauses 6.1, 6.2, 5.1 or 2 of the Code on this point.

(C) Improvements in Quality of Life webpage

Claim 4
"*Starting ENTRESTO can lead to substantial improvements in social and physical activities comparable to feeling 9 YEARS YOUNGER vs ACEi (enalapril):**"*

- As explained above, the primary endpoint of the pivotal PARADIGM-HF trial showed that Entresto was superior to enalapril in reducing the rates of death from cardiovascular causes or hospitalisation for heart failure (the composite primary end point) and death from any cause among patients with heart failure and a reduced ejection fraction[5]. The Code stated that "claims should not be qualified by the use of footnotes". Since the primary endpoint was met, and that it was not unacceptable to use a secondary analysis to support a claim as long as it was not misleading, stating the fact this is a secondary analysis in the footnote was not unacceptable, and would not be qualifying the claim or materially changing the way a health professional interprets the information.

- A pre-defined secondary endpoint in PARADIGM-HF was the change from baseline to 8 months in the clinical summary score on KCCQ (a QoL measure) and this endpoint was met demonstrating that Entresto was superior to enalapril. This secondary endpoint supported the section of the claim "substantial improvements in social and physical activities" The post hoc analysis data was also supportive of this as seen below:

    - In a post-hoc secondary analysis of 8399 patients from the PARADIGM-HF trial, limitations in physical and social activities were significantly improved in almost all domains in patients randomised to receive Entresto, compared with enalapril.

- Given that the primary endpoint of the PARADIGM-HF trial was met, and that Entresto demonstrated superiority vs Enalapril on rates of death and hospitalisation, it was not unacceptable to use secondary endpoints or post hoc data to support the claims that Entresto demonstrated improvements in QoL vs Enalapril as it was not misleading.

- Novartis did not seek to hide information in the footnotes to Claim 4. The footnote stated the primary endpoint of the PARADIGM-HF trial, which was met. Therefore, there had been no breach of Clauses 6.1, 6.2, 5.1 or 2 of the Code on this point.

3. Conclusion

Novartis submitted that using secondary endpoints or secondary analyses to support claims was not unacceptable, as long as it supported the primary findings and did not mislead the reader.

Considering the above, Novartis' opinion was that none of the Clauses had been breached as described above. High standards had been maintained by Novartis and Novartis fully refuted any breaches of Clauses 5.1, 6.1, 6.2 and 2 of the Code.

PANEL RULING

The Panel noted that the Entresto webpages in question appeared to be accessible within the Medicines > Cardio-Metabolic section of the health.novartis.co.uk website.

Claim 1: Improve the chronic HFrEF patient's experience vs ACEi (enalapril) - improvements in quality of life

The Panel noted that this claim appeared on the home webpage.

Beneath a banner, the sub-heading 'Entresto (sacubitril/valsartan) was followed by 'For patients living with chronic heart failure, time is essential, so start with ENTRESTO (sacubitril/valsartan)'. The webpage then had two distinct highlighted sections for newly diagnosed and previously diagnosed patients, followed by a list of five prominent claims each within a highlighted banner which included to the right of the banner a statement that appeared to be linked to relevant webpages. The claim in question 'Improve the chronic HFrEF patient's experience vs ACEi (enalapril)' featured within one of the five banners with the phrase 'Improvements in quality of life' in an outline box to the right which was linked to relevant webpages. The Panel noted Novartis' submission that clicking on this button led to a webpage which explained the improvements in social and physical activities compared to enalapril and that 'patient experience' covered a range of measures including improvements in sexual relationships, hobbies and recreation, household chores, gardening, and how patients feel compared to ACEi (enalapril).

The Panel noted that the webpage in question appeared to be akin to a contents page directing readers to relevant parts of the website. The Panel noted that nonetheless claims on the page had to be capable of standing alone in relation to the requirements of the Code. The claim in question was a very general claim for improvement in quality of life; the Panel noted that the complainant did not state or imply that there was no improvement with Entresto compared to enalapril or that the evidence in this regard was equivocal. In this context, the Panel considered that failing to provide the exact patient experience benefits adjacent to or below the claim 'Improve the chronic HFrEF patient's experience vs ACEi (enalapril)' did not mean that it was misleading or unqualified as alleged.

The Panel further noted the allegation that 'patient experience' was very broad and could mean a number of clinical outputs in the cardiology space. In the Panel's view, it was clear that the patient experience in the claim 'Improve the chronic HFrEF patient's experience vs ACEi (enalapril)' was referring to 'improvements in quality of life', the phrase which appeared immediately to the right within the banner as a button and which would likely be understood as multifactorial.

The Panel, noting its comments and views above, did not consider that the complainant had established that the claim 'Improve the chronic HFrEF patient's experience vs ACEi (enalapril) Improvements in quality of life' was unqualified and thereby misleading, or ambiguous in relation to the meaning of the phrase 'patient experience' as alleged and ruled **no breach of Clause 6.1.**

With regard to the allegation that it was not made clear that quality of life was not a primary endpoint in trials comparing Entresto vs Enalapril but was part of a secondary endpoint analysis and post-hoc analysis, and that primary endpoints were not given, the Panel noted Novartis' submission about the endpoint data in the PARADIGM-HF trial and the post hoc analysis above. The Panel noted that the quality of life data was derived from a secondary endpoint and a post hoc analysis. The Panel noted that Novartis also referred to an exploratory analysis in relation to quality of life data but noted that this did not appear to have been used to substantiate any part of the claim at issue and had not been provided to the Panel. The Panel noted that the primary endpoint in the PARADIGM-HF trial had been met. The Panel noted that it was not necessarily unacceptable to promote on the basis of secondary endpoint data; its acceptability depended on a number of factors including the context and nature of the trial. Whether the primary endpoint was met might be relevant.

The Panel noted Novartis' submission about a footnote to the claim in question on the Entresto homepage, along with footnotes on the linked page which was viewed when 'improvements in quality of life' was clicked. Novartis submitted that the footnotes to the claim in question on the Entresto homepage explained the study designs of the Chandra publication and the Lewis publication. Further, that the linked webpage dedicated to the improvements in quality of life stated the primary endpoint of the PARADIGM-HF trial clearly along with the nature of the analyses that supported the claims on this page. In this regard, the Panel noted that the home page must be capable of standing alone with regard to the requirements of the Code and a footnote on a separate linked page would therefore, in the Panel's view, not be relevant when determining the acceptability of a claim on the home page. Contrary to Novartis' submission the Panel could not find the associated footnotes to the claim at issue on the Entresto home page that explained the study designs of the Chandra and Lewis publications. The only reference appeared, to the Panel, to be in the list of references which included a reference to Lewis et al (2017) and Chandra et al (2018) for which no study titles were given nor details of the study design.

In any event, the Panel noted that if information in a footnote was required to ensure that a main claim complied with the Code then that information should be part of the claim or in its immediate visual field. Information that was supplementary to the claim but not required for Code compliance could appear in the footnote or similar.

In the Panel's view, noting its comments above, the complainant had not established in relation to the claim 'Improve the chronic HFrEF patient's experience vs ACEi (enalapril) - improvements in quality of life', as it appeared on the home page, that the omission of the primary endpoint and the failure to make it clear that the quality of life data was derived from a secondary endpoint and post hoc analysis was misleading and contrary to the requirements of Clause 6.1**.** **No breach of Clause 6.1** was ruled**.**

The complainant had cited Clause 6.2 but had not made any allegation with regard to substantiation. The complainant bore the burden of proof; it was not for the Panel to infer reasons on the complainant's behalf. The Panel therefore ruled **no breach of Clause 6.2.**

The Panel, noting its no breach rulings above, consequently ruled **no breach of Clauses 5.1 and 2.**

Claim 2: National guidelines support ENTRESTO as a 1st line treatment option in chronic HFrEF

The Panel noted that this claim at issue appeared within a banner on the Entresto home page beneath claim 1 above.

With regard to the complainant's allegation that the claim at issue was inaccurate and misleading as Entresto was recommended when LVEF was less than 40% by the Heart failure Hub Scotland Guidelines, Novartis submitted that the universal definition of HFrEF was heart failure with an ejection fraction of <40%, which was also reflected within the definition of terms in the UK NICE guideline and was consistent with other UK, European and American Guidelines. Novartis submitted the audience of this website were healthcare professionals or decision-makers, who would understand the meaning of HFrEF, so further qualification, definition or explanation was not necessary. Use of the word "option" in the claim in question highlighted that other medicine options remain available, according to Novartis.

The Panel noted Novartis' submission that the Heart failure Hub Scotland Guidelines referred to by the complainant, which the Panel noted was titled 'NHS Scotland Heart Failure Transition and Recovery Plan in response to COVID-19 (25th May 2020)' stated 'Select, where possible and where appropriate, therapies that require the fewest titration steps eg. Bisoprolol as BB of choice and Sacubitril Valsartan as RAASi of choice when left ventricular ejection fraction (EF) is less than 40%'. The Panel also noted Novartis' submission in relation to the definition of reduced ejection fraction in the UK NICE guidelines and the consistency of the definition across other European and American guidelines. In this regard, the Panel noted the UK NICE guideline referred to the Entresto NICE appraisal which recommended Entresto for use where, amongst other things, patients had a LVEF of 35% or less (1.4.22); under the glossary of terms used in the guideline, the Panel noted 'Heart failure with reduced ejection fraction' was defined as below 40%. The Panel also noted that the ESC guidelines and the 2022 AHA/ACC/HFSA guideline for the management of heart failure referred to HFrEF of ≤ 40% as opposed to <40% as stated by Novartis.

The Panel noted Clause 6.1 stated, amongst other things, that material must be sufficiently complete to enable recipients to form their own opinion of the therapeutic value of the medicine.

The Panel noted that the guidelines provided were largely consistent about the classification of heart failure. The Panel noted that the degree of reduced ejection fraction was not part of the licenced indication which simply referred to heart failure with reduced ejection fraction. The Panel noted that the certificate for the webpage in question listed the audience as 'Physician; Pharmacist; Payor / Health Insurance / Nurse / Other Healthcare Stakeholder'. In the Panel's view, it was unlikely that such a broad audience would all be aware that the definition of HFrEF was less than 40% LVEF as stated by Novartis or would all have a consistent understanding of its meaning. The Panel, thus, on balance, considered that the claim, without clarification of the degree of reduced ejection fraction, was not sufficiently complete such that the broad readership could properly understand the term as reflected in the guidelines. **A breach of Clause 6.1** was ruled.

The Panel noted the complainant cited Clause 6.2 but made no allegation nor provided any reasons to support the citation. It was not for the Panel to infer such reasons on behalf of the complainant who bore the burden of proof. The Panel therefore did not consider the

complainant had established that the claim was incapable of substantiation and ruled **no breach of Clause 6.2**.

The Panel noted its ruling of a breach of Clause 6.1 above and, bearing in mind the broad target audience for the webpages which sat on the health.novartis.co.uk website, considered that Novartis had, on balance, failed to maintain high standards in this regard. A **breach of Clause 5.1** was ruled.

The Panel considered Clause 2 was a sign of particular censure and did not consider that the particular circumstances of this case warranted such a ruling. **No breach of Clause 2** was ruled.

Claim 3: Patients on ENTRESTO feel better, stay out of the hospital, and live longer vs ACEi (enalapril)

The Panel noted the complainant's allegation that it was not made clear that the claim was not entirely based on all primary endpoint data and that some clinical outcomes mentioned in this claim were based on post-hoc analyses which was misleading and not made clear by Novartis.

The Panel noted that the claim at issue appeared on the HFrEF Chronic Disease Trajectory webpage and appeared within a highlighted banner as the title to a graph adapted from Gheorgiade et al (2015) which depicted cardiac function and quality of life against disease progression. The data line was labelled in relation to diagnosis and hospitalisation through to chronic decline and mortality. The data line in relation to transition and hospitalisation was labelled as deriving from the Pioneer-HF trial and the PARADIGM-HF trial respectively. Beneath 3 banners very brief details of 5 trials, including the PARADIGM-HF and Pioneer-HF trial, were given. Towards the bottom of the page, a footnote to the graph gave study details (Pioneer-HF and PARADIGM-HF) including endpoints but did not include details of the quality of life endpoints. The Panel noted that the claim in question was referenced to the Entresto summary of product characteristics and six studies including the Paradigm and the Pioneer-HF trials. The claim in question was referenced to the post hoc analysis, Chandra et al.

The Panel noted Novartis' submission that the claim was fully substantiated. 'Patients on ENTRESTO feel better' referred to quality of life and was also supported by formal QoL assessment in the PARADIGM-HF trial. 'Stay out of the hospital, and live longer vs ACEi (enalapril)', according to Novartis, referred to a reduction in mortality and hospitalisation seen in the PARADIGM study; the data supported this aspect of the claim fully and since the primary endpoint was met, stating the information in the footnote was not an attempt by Novartis to 'hide' this information.

The Panel noted Novartis' submission that specifically, the trial demonstrated that Entresto was superior to enalapril in reducing the risks of death and of hospitalisation for heart failure and as compared with enalapril, Entresto also decreased the symptoms and physical limitations of heart failure (P = 0.001); the primary endpoint in the study was a composite of death from cardiovascular causes or hospitalization for heart failure whilst one of the secondary endpoints was the change from baseline to 8 months in the clinical summary score on KCCQ (a QoL measure). Novartis submitted that this claim was based on a combination of endpoints and both of these endpoints were met.

Whilst the Panel queried whether an improvement in quality of life could necessarily be translated to patients feeling better as claimed by Novartis, the Panel noted the complainant's allegations solely related to it not being made clear that the claim was not entirely based on primary endpoint data and that some clinical outcomes mentioned in the claim were based on post-hoc analyses which was misleading. Novartis submitted that the claim in its entirety was supported by the PARADIGM-HF trial and that the post hoc analyses were supportive to the findings in the PARADIGM-HF trial (where primary and secondary endpoints were met demonstrating superiority in reduced hospitalisations and improved symptoms and physical activity on the KCCQ), hence use of these analyses were not misleading.

The Panel noted its comments above at claim one in relation to the use of primary and secondary endpoint data and considered that these were relevant here. The Panel did not consider that the complainant, who bore the burden of proof, had established why the status of the endpoint data and that certain data derived from a post hoc analysis should have been made clear in relation to the claim and that the failure to do so was misleading. The Panel accordingly ruled **no breach of Clause 6.1** of the Code.

The Panel noted Novartis' submission that the claim could be qualified by the PARADIGM-HF trial and the post-hoc analysis was supportive of the data. The Panel noted that the complainant had cited Clause 6.2 but made no allegation nor provided any reasons to support the citation. It was not for the Panel to infer such reasons on behalf of the complainant who bore the burden of proof. The Panel therefore did not consider the complainant had established that the claim was incapable of substantiation and ruled **no breach of Clause 6.2**.

Noting it's no breach rulings above the Panel consequently **ruled no breach of Clauses 5.1 and 2.**

Claim 4: Starting ENTRESTO can lead to substantial improvements in social and physical activities comparable to feeling 9 YEARS YOUNGER vs ACEi (enalapril)*

The Panel noted that the claim in question appeared on the Quality of Life webpage within a banner that featured a depiction of a couple standing side by side to illustrate sexual relationships, and differing depictions for hobbies and recreation, household chores and gardening.

With regard to the allegation that the claim in question was a secondary and not primary endpoint, and the use of an asterix hid that this was not a primary endpoint, the Panel noted Novartis' submission that since the primary endpoint was met, it was not unacceptable to use a secondary analysis to support a claim as long as it was not misleading and that stating the fact this is a secondary analysis in the footnote is not unacceptable, and would not be qualifying the claim or materially change the way a health professional interprets the information.

The Panel noted the associated footnote to the asterix stated 'as measured by an analysis model that incorporated age and treatment effect' and went on to describe this as a secondary analysis of the clinical trial, PARADIGM-HF, with improvements in physical and social activities compared to the enalapril group; Novartis submitted this was supported by post hoc analysis data where an analysis of 8399 patients from the PARADIGM-HF trial significantly improved limitations in physical and social activities in almost all domains in patients randomised to receive Entresto, compared with enalapril. The associated footnote also stated the primary endpoint.

The Panel noted its comments above at claim 1 about the use of primary and secondary endpoints and considered that they applied here. In the Panel's view, it was not necessarily unacceptable to make claims based on secondary endpoints from a study. In principle, when a primary endpoint failed to achieve statistical significance, it was also not necessarily unreasonable to refer to secondary endpoint data so long as this was placed within the context of the overall study findings. The Panel did not consider that the use of the asterix which stated that the claim was based on a secondary analysis of PARADIGM-HF meant that the claim in question hid that it was not based on primary endpoint data. The Panel did not consider that the claim in question was misleading on the narrow ground alleged and ruled **no breach of Clause 6.1.**

The Panel noted the complainant cited Clause 6.2 but made no allegation nor provided any reasons to support the citation. It was not for the Panel to infer such reasons on behalf of the complainant who bore the burden of proof. The Panel therefore did not consider the complainant had established that the claim in question was incapable of substantiation and ruled **no breach of Clause 6.2**.

Noting its no breach rulings above the Panel consequently **ruled no breaches of Clauses 5.1 and 2**.

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Complaint received **24 June 2022**

Case completed **1 August 2023**