CASE AUTH/3633/4/22

COMPLAINANT v NOVARTIS

Allegations about misleading information for Entresto on Novartis' website

CASE SUMMARY

This case was in relation to allegations that the 'Starting and Monitoring Entresto' page of the Entresto (sacubitril/valsartan) promotional website contained misleading information and omitted important safety information.

The Panel ruled a breach of the following Clauses of the 2021 Code as it considered that by providing some, but not all, the relevant information in relation to hepatic impairment and renal impairment in a section of the webpage which was intended to advise health professionals on considerations when using the medicine, was misleading:

Breach of Clause 6.1	**Providing misleading information**
Breach of Clause 5.1	**Failing to maintain high standards**
Breach of Clause 2	**Bringing discredit upon, and reducing confidence in the pharmaceutical industry**

The Panel ruled no breach of the following Clauses of the 2021 Code on the basis that the complainant had not demonstrated that:

- **health professionals would be misled by the claim 'Monitoring and using Entresto is simple' or that the claim, in the context of the particular webpage at issue, could not be substantiated;**
- **based on the very narrow allegation, the omission of liver function monitoring in the monitoring section of the webpage was misleading, noting the Entresto SPC did not specifically state that liver function should be monitored:**

No Breach of Clause 6.1	**Requirement that claims and information must not be misleading**
No Breach of Clause 6.2	**Requirement that claims must be capable of substantiation**

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

FULL CASE REPORT

An anonymous, contactable complainant who described him/herself as a cardiac specialist complained about misleading information regarding Entresto (sacubitril/valsartan) on Novartis' website.

COMPLAINT

The complainant provided a link to alleged misleading information presented on a Novartis promotional webpage regarding monitoring requirements for Entresto (ref 145885, October 2021). The complainant explained that towards the end of the page, there was a claim 'Monitoring and using ENTRESTO is simple'. There was the option to click further into this statement which then opened up 3 notepads which read 'prior to initiation', 'after dose escalation' and 'ongoing'. However, in any of these areas, the need for liver function monitoring was not mentioned. The summary of product characteristics (SPC) of Entresto specifically stated:

> 'Hepatic impairment - No dose adjustment is required when administering Entresto to patients with mild hepatic impairment (Child-Pugh A classification). There is limited clinical experience in patients with moderate hepatic impairment (Child-Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. Entresto should be used with caution in these patients and the recommended starting dose is 24 mg/26 mg twice daily (see sections 4.4 and 5.2). Entresto is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification) (see section 4.3).'

The complainant alleged that it was misleading and a risk for clinicians to have information about hepatic monitoring hidden and not mentioned. The complainant alleged that this was really poor from Novartis and that whoever had approved this promotional content must have been inexperienced in the cardiology space/approval process.

The complainant alleged that, in addition, renal function aspects were not clearly laid out in this monitoring section as the contraindications stated, 'Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2) (see sections 4.4 and 4.5)'. The complainant alleged that even the claim 'monitoring Entresto was simple' was false as monitoring renal function, liver function, electrolytes etc around the medicine was a complex aspect of heart failure monitoring and was not simple as implied. The complainant alleged that Novartis had not taken patient safety seriously and had brought discredit to the industry with the content on this page. By not detailing the exact requirements with hepatic impairment and renal function contraindications, this was below the required standards. The complainant alleged breaches of the following clauses due to misleading and inaccurate claims alongside not providing full information to allow for informed prescribing choice: Clauses 6.1, 6.2, 5.1 and 2.

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

RESPONSE

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

Background

Novartis submitted that it maintained a website containing information pages on its medicines aimed at UK health professionals. Each time a health professional accessed the website they were asked to confirm that they were a UK health professional audience (or relevant NHS decision maker). On this website, there was a dedicated section on Entresto. In this sub-section, Novartis maintained a page called 'Starting and monitoring Entresto'. The complaint related to this page. Novartis provided screenshots showing how the website was accessed and specific sections of the page relevant to the complaint.

Novartis' response to specific complaints

Responses are given for the specific complaints:

'Simple' monitoring claim

Novartis submitted that:

- The claim 'Monitoring and using ENTRESTO is simple' was located immediately above the visual of notepads which outlined key elements of monitoring, including renal function and electrolytes, for both ACE inhibitors and Entresto.
- The monitoring requirements for ACE inhibitors, which were routinely used in clinical practice, were similar in all key elements to those for Entresto. Therefore, it was reasonable to claim that monitoring was simple, as there was nothing additional to consider vs ACE inhibitors. This comparison was also stated, earlier on the same 'Starting and Monitoring Entresto' webpage and therefore usually read immediately prior, 'Starting and monitoring patients on ENTRESTO is as simple as with ACEi (enalapril)'.
- The claim was referenced to the SPC for Entresto and there was a direct link to this in references and a direct prominent link at the head of the webpage to prescribing information. Therefore, additional information to provide additional details and support safe and appropriate prescribing were easily accessible.
- Most guideline-indicated medicines used for treating heart failure (eg ACEi/ARBs, loop diuretics and mineralocorticoid receptor antagonists) had recommendations for the monitoring of renal function and electrolyte imbalances therefore this was routine practice in these patients and would be familiar to prescribers.
- Novartis submitted that this claim was accurate in the positioned context, not misleading, fully substantiated by the SPCs and denied a breach of Clauses 6.1 and 6.2.

Liver function monitoring not mentioned

Novartis submitted that:

- Monitoring of liver function was not a specific requirement of Entresto use.
- The relevant caution to reduced dose when prescribing in those with moderate hepatic impairment or elevated liver function tests was clearly summarised in the section 'Considerations when using ENTRESTO' on the same 'Starting and Monitoring Entresto' page. Further qualification on the definition of moderate hepatic

impairment was given in a footnote. In the same table mild liver impairment was stated for standard dosing and therefore implicitly severe liver impairment was excluded. This 'Considerations when using ENTRESTO' tab was directly under the tab 'Monitoring and using Entresto is simple'. A plus (+) sign was on the right-hand side of the tab showed clearly that the tab was expandable, therefore this information was not hidden.

- In the 'Monitoring and using Entresto is simple' visual below there was a clear statement to 'Consider concomitant medications and contraindications' prior to initiation. This was referenced to the SPC for Entresto with a direct link provided along with a direct prominent link to prescribing information at the head of the webpage. 'Severe hepatic impairment, biliary cirrhosis and cholestasis' was listed under the contraindications for Entresto.
- Given there was no requirement for liver function monitoring with Entresto and information on initiating in those with liver impairment, was summarised in the subsequent 'Considerations when using Entresto' section, along with direct links to the SPC and prescribing information, this information was not hidden and supported appropriate prescribing and patient safety. Novartis denied a breach of Clauses 6.1, 6.2, 5.1 or 2 on this point.

Renal function monitoring and prescribing in those with renal impairment/selected contraindications not clearly laid out

The complainant also alleged that renal function aspects were not clearly laid out in this monitoring section either as the contra-indications stated, 'Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment'.

Novartis submitted that:

- With regard to monitoring renal function in the 'Monitoring and using Entresto is simple' visual, there was a clear indication that renal function monitoring was required at all stages (prior to initiation, after dose escalation and ongoing). This was referenced to the SPC for Entresto with a direct link provided along with a direct prominent link to prescribing information at the head of the webpage which provided additional detail on monitoring requirements including renal function. In the subsequent 'Considerations when using ENTRESTO' section there was a clear visual and text indicating that Entresto could impact renal function.
- With regard to initiating in those with renal impairment, the caution in moderate/severe renal impairment was stated 'Considerations when using ENTRESTO'. This summarised the need for lower dosing and, in the footnote, reinforced the need for caution in severe renal impairment.
- For other contraindications such as with 'aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment', there was a clear statement to 'Consider concomitant medications and contraindications' prior to initiation as described and illustrated previously. This was referenced to the SPC for Entresto with a direct link provided along with a direct prominent link to prescribing information at the head of the webpage.
- There was no requirement in the Code to reference every contraindication to a medicine. Aliskiren had limited use in the UK as it was not approved by relevant Arterial hypertension (HTA) bodies and itself had clear warnings around use with

other medications affecting the Renin-Angiotensin-Aldosterone System (RAAS) pathway, such as Entresto. As such, Novartis decided that it was not necessary to reference Aliskiren specifically on the webpage.

- Therefore, Novartis believed that renal function monitoring requirements were clear and information was provided to support safe and appropriate prescribing in those with renal impairment and contraindications to use such that it denied a breach of Clauses 6.1, 6.2, 5.1 or 2 on this point.

Approval

- Novartis submitted that the signatory who approved the material was a qualified medical doctor with extensive signatory experience in the pharmaceutical industry. He/she had worked with the company for many years in the cardiovascular therapy area.
- All signatories underwent regular training and were required to complete a formal assessment before being named as a signatory.
- Therefore, Novartis had confidence that the signatory was appropriately qualified and experienced in both Novartis' approval process and the cardiovascular area and, as such, high standards had been maintained and there had been no breach of Clause 5.1 on this point.

Conclusion

Novartis refuted the allegations and felt all claims were adequately supported, key elements of initiation and monitoring were detailed to ensure clinicians had adequate information, patient safety was maintained and the material was approved by an appropriate individual. Novartis denied a breach of Clauses 6.1, 6.2, 5.1 and 2.

PANEL RULING

The Panel noted the layout of the promotional webpage at issue. Beneath the heading 'Starting and monitoring Entresto' were the claims 'Starting and monitoring patients on Entresto is as simple as with ACEi (enalapril)' and 'Flexible starting doses tailored to your patients' needs, with titration similar to ACEi (enalapril)'. Beneath these claims were three Entresto packshots and further information including claims in relation to two clinical trials where Entresto had been compared with enalapril, followed by an invitation to download the clinical trial summaries. This was followed by three expandable sections titled 'Monitoring and using Entresto is simple', 'Considerations when using Entresto', and 'Who is suitable for Entresto?'. A link to the prescribing information was included near the top of the webpage and a link to safety information appeared towards the bottom of the webpage, in very small font, immediately before a list of footnotes and references. The Panel did not have before it the content accessible from the prescribing information and safety information links on the webpage. The references section included a link to the Entresto SPC.

Claim 'Monitoring and using Entresto is simple'

The Panel noted the complainant's allegation that the claim 'monitoring Entresto is simple' was false as monitoring renal function, liver function and electrolytes, etc with Entresto was a complex aspect of heart failure monitoring and was not simple as implied.

The Panel noted that the claim in question 'Monitoring and using Entresto is simple' was the title of one of the expandable sections referred to above. The Panel further noted that the webpage in question, as described above, had a particular focus on comparing Entresto with the ACE inhibitor enalapril and contained numerous references to enalapril being the comparator used in clinical trials and in clinical practice.

The Panel noted that, when expanded, the 'Monitoring and using ENTRESTO is simple' section featured three notepads titled 'Prior to initiation', 'After dose escalation' and 'Ongoing' which compared the monitoring requirements for ACE inhibitors with those for Entresto. The Panel further noted Novartis' submission that the monitoring requirements for ACE inhibitors, routinely used in clinical practice, were similar in all key elements to those for Entresto.

Clause 6.1 required, amongst other things, that claims must not mislead either directly or by implication, by distortion, exaggeration or undue emphasis and material must be sufficiently complete to enable recipients to form their own opinion of the therapeutic value of the medicine; Clause 6.2 required information, claims and comparisons to be capable of substantiation.

The Panel considered the immediate and overall impression of the claim 'Monitoring and using Entresto is simple' to a busy health professional. On balance, and noting the content and layout of the webpage, the Panel considered that a health professional would likely read the claim in the context of the monitoring required with an ACE inhibitor compared with Entresto, particularly given the claim 'Starting and monitoring patients on Entresto is as simple as with ACEi (enalapril)' at the beginning of the webpage and the numerous comparative references between the two medicines. Thus, on balance, the Panel considered that the complainant had not demonstrated that health professionals would be misled by the claim 'Monitoring and using Entresto is simple', or that the claim, in the context of the particular webpage at issue, could not be substantiated and therefore the Panel ruled **no breach of Clauses 6.1** and **6.2**.

Liver function monitoring

The Panel noted the complainant's allegation that the need for liver function monitoring was not mentioned on any of the three notepads titled 'Prior to initiation', 'After dose escalation' and 'Ongoing' and that it was misleading and a risk for clinicians to have information about hepatic monitoring hidden and not mentioned.

The Panel noted the hepatic considerations for Entresto in the SPC included that patients with hepatic impairment were mentioned as a special population in Section 4.2 which stated:

> 'No dose adjustment is required when administering Entresto to patients with mild hepatic impairment (Child-Pugh A classification). There is limited clinical experience in patients with moderate hepatic impairment (Child-Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. Entresto should be used with caution in these patients and the recommended starting dose is 24 mg/26 mg twice daily (see sections 4.4 and 5.2). Entresto is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification) (see section 4.3).'

In addition, Section 4.4 contained the following special warning and precaution for use in patients with hepatic impairment:

> 'There is limited clinical experience in patients with moderate hepatic impairment (Child-Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. In these patients, exposure may be increased and safety is not established. Caution is therefore recommended when using it in these patients (see section 4.2 and 5.2). Sacubitril/valsartan is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification) (see section 4.3).'

Section 4.3 of the SPC listed contraindications to use of Entresto and included, amongst other things, severe hepatic impairment, biliary cirrhosis and cholestasis.

Turning to the promotional material at issue, the Panel noted that within the 'Prior to initiation' notepad it stated, 'consider concomitant medications/contraindications'; there was no specific reference to hepatic impairment. Beneath the notepads, within the expandable 'Considerations when using Entresto' section, was a table titled 'Dosing considerations'. This table included that standard dosing was indicated for patients with mild liver impairment and that low dosing was indicated for patients with moderate liver impairment or with AST/ALT values more than twice the ULN, followed by a double asterisk, which led to a very small footnote towards the bottom of the page which stated 'Moderate hepatic impairment: Child-Pugh B classification'. The Panel noted Novartis' submission that monitoring of liver function was not a specific requirement of Entresto use and further that the Entresto SPC did not contain a requirement to monitor liver function.

Noting that the Entresto SPC did not specifically state that liver function should be monitored, the Panel considered that the complainant had not established that the omission of liver function monitoring in the notepads in the monitoring section of the webpage was misleading as alleged and based on the very narrow allegation, the Panel ruled **no breach of Clause 6.1**.

Whilst the Panel noted that there was no specific requirement to monitor liver function in the Entresto SPC, its use in hepatic impairment was one area where there were important clinical differences between the SPCs for Entresto and Enalapril. The Panel considered that in the light of the emphasis within the promotional material on the similarities between Entresto and ACE inhibitors, such as Enalapril in their monitoring and use, it would have been prudent to also highlight within the material that there were important differences.

The Panel disagreed with Novartis' submission that as information about use in mild and moderate liver impairment had been included, it was implicit from the table that use in severe hepatic impairment was excluded. The Panel considered that stating that low dosing was indicated for patients 'with moderate liver impairment or with AST/ALT values more than twice the ULN' without also stating that Entresto was contraindicated in severe hepatic impairment was misleading; AST/ALT values more than twice the ULN would also include patients with severe hepatic impairment. Nowhere on the webpage was it stated that Entresto was contraindicated in severe hepatic impairment.

The Panel noted that links to the prescribing information and SPC were provided on the webpage but considered that the size and location of these links, and lack of direction towards them in the relevant sections, was such that a health professional might overlook them and would have to search the website to find additional relevant safety information.

The Panel considered that whether a contraindication needed to be highlighted within a particular section of promotional material, in addition to its requirement to be included within the

prescribing information that was required on all promotional material, depended on a consideration of all of the circumstances including the nature of the contraindication and the content, layout, audience and intended use of the material.

Given the information on mild and moderate hepatic impairment within the 'Considerations when using Entresto' section of the webpage, a health professional would likely expect that all the relevant information in relation to hepatic impairment would be stated in the body of the webpage, which was not so; the misleading impression given was compounded by reference to low dosing in patients with AST/ALT values more than twice the ULN without further clarification that it was contraindicated in patients with severe hepatic impairment. The Panel considered that by providing some, but not all, the relevant information in relation to hepatic impairment in a section of the webpage which was intended to advise health professionals on considerations when using the medicine, was misleading and **a breach of Clause 6.1** was ruled.

Renal function monitoring

The Panel noted the allegation that renal function aspects were not clearly laid out in the monitoring section and that concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m^2) was contraindicated in the Entresto SPC.

In addition to the above contraindication, the Panel noted that the Entresto SPC further stated, in Section 4.2, under the subheading, '*Renal impairment*':

> 'No dose adjustment is required in patients with mild (Estimated Glomerular Filtration Rate [eGFR] 60-90 ml/min/1.73 m^2) renal impairment. A starting dose of 24mg/26mg twice daily should be considered in patients with moderate renal impairment (eGFR 30-60 ml/min/1.73 m^2). As there is very limited clinical experience in patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) (see section 5.1) Entresto should be used with caution and a starting dose of 24mg/26mg twice daily is recommended. There is no experience in patients with end-stage renal disease and use of Entresto is not recommended.'

Further specific advice for patients with impaired renal function and those with worsening renal function was included in Section 4.4, '**Special warnings and precautions for use**', which stated:

> 'Impaired renal function
>
> Evaluation of patients with heart failure should always include assessment of renal function. Patients with mild and moderate renal impairment are more at risk of developing hypotension (see section 4.2). There is very limited clinical experience in patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) and these patients may be at greatest risk of hypotension (see section 4.2). There is no experience in patients with end-stage renal disease and use of sacubitril/valsartan is not recommended.
>
> Worsening renal function
>
> Use of sacubitril/valsartan may be associated with decreased renal function. The risk may be further increased by dehydration or concomitant use of non-steroidal anti-inflammatory

agents (NSAIDs) (see section 4.5). Down-titration should be considered in patients who develop a clinically significant decrease in renal function.'

The Panel noted Novartis' submission that the 'Monitoring and using Entresto is simple' section included that renal function monitoring was required at all stages (prior to initiation, after dose escalation and ongoing) and that within each notepad renal function monitoring was referenced to the SPC which was available via a link. The Panel noted that the link to the SPC was not in the section in question but within the references section towards the bottom of the page. The Panel noted Novartis' submission that a link to prescribing information was included at the head of the webpage and that both the SPC and the prescribing information included the additional detail on monitoring requirements including renal function.

The Panel considered that whether a contraindication or special warning/precaution needed to be highlighted within a particular section of promotional material, in addition to its requirement to be included within the prescribing information that was required on all promotional material, depended on a consideration of all of the circumstances including the nature of the contraindication/warning/precaution and the content, layout, audience and intended use of the material.

The Panel noted that links to the prescribing information and SPC were provided on the webpage,but considered that the size and location of these links, and lack of direction towards them in the relevant sections, was such that a health professional might overlook them and would have to search the website to find additional relevant safety information.

The Panel noted that the 'Considerations when using Entresto' section stated that standard dosing was indicated for patients with mild renal impairment and low dosing was indicated for patients with moderate/severe renal impairment which included an asterisk which was associated with a very small footnote towards the bottom of the webpage which stated 'Use with caution in patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2)'.

The Panel noted that the supplementary information to Clause 6.1 stated that, in general, claims should not be qualified by the use of footnotes and the like. The Panel considered that this footnote contained important and relevant safety information which should have been stated alongside the information about low dosing in severe renal impairment.

The considerations section of the webpage also stated, under the heading 'RENAL FUNCTION, Consider down-titration in clinically relevant cases', however, there was no reference to other important clinical information in this regard including that section 4.4 of the SPC stated that there was no experience in patients with end-stage renal disease and use of Entresto was not recommended in such patients.

Furthermore, there was no reference to the contraindication with aliskiren-containing medicinal products in patients with diabetes mellitus or renal impairment (eGFR <60 ml/min/1.73 m^2). The Panel disagreed with Novartis' submission that as aliskiren was not approved by relevant HTA bodies, then it was not necessary to reference the aliskiren contraindication specifically; in the Panel's view, if that contraindication was relevant to some patients, then health professionals needed to be made aware, particularly as the material in question was advocating use of a low dose of Entresto in moderate/severe renal impairment.

Given the information on renal function/renal impairment in the 'Considerations when using Entresto' section of the webpage, a health professional would likely expect that all the relevant information in relation to renal impairment would be stated in the body of the webpage, which was not so. The SPC had additional important and relevant safety information including that Entresto was not recommended in patients with end-stage renal disease and that concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m^2) was contraindicated. The Panel considered that by providing some, but not all, the relevant information in relation to renal impairment in a section of the webpage which was intended to advise health professionals on considerations when using the medicine, was misleading and **a breach of Clause 6.1** was ruled.

Overall

The Panel noted its rulings of breaches of the Code above, including in relation to matters of patient safety, and considered that Novartis had failed to maintain high standards and **a breach of Clause 5.1** was ruled.

Clause 2 was a sign of particular censure and was reserved for such use. The supplementary information to Clause 2 included prejudicing patient safety as an example of an activity that was likely to be in breach of this clause.

The Panel considered that patient safety was of the utmost importance and that health professionals should be able to rely on company produced material to be complete and unambiguous in this regard. The Panel considered that by providing some, but not all, the relevant information in relation to renal and hepatic impairment in the body of a webpage which was intended to advise health professionals on considerations when using the medicine, was such that Novartis had reduced confidence in, and brought discredit upon, the industry and **a breach of Clause 2** was ruled.

Complaint received **13 April 2022**

Case completed **27 April 2023**