CASE AUTH/3655/6/22

ANONYMOUS HEALTH PROFESSIONAL v NOVARTIS

Alleged promotion of Mayzent

CASE SUMMARY

This case was in relation to the promotion of Mayzent (siponimod) on the 'Dosing and administration' page on a Novartis website.

The Panel ruled a breach of the following Clauses of the 2021 Code for referring to Mayzent initiation in patients with a history of myocardial infarction and heart failure without making apparent the absolute contra-indication in patients with a history of myocardial infarction or heart failure in the previous 6 months, except on a separate webpage and within the prescribing information which, in the Panel's view, was insufficient to negate this immediate misleading impression:

Breach of Clause 6.1	**Providing misleading information**
Breach of Clause 6.2	**Providing a misleading impression which was incapable of substantiation**
Breach of Clause 5.1	**Failure 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 as it did not consider that highlighting the contraindication in pregnancy for Mayzent meant that health professionals would assume there would be no other considerations or contraindications:

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 about the promotion of Mayzent (siponimod). Mayzent was indicated for the treatment of adult patients with secondary

progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity.

COMPLAINT

The complainant stated that he/she was submitting an anonymous complaint in view of the systemic challenges around the very low compliance culture at Novartis. The complaint was centred around promotion of Mayzent on the health.novartis.co.uk website (UK | January 2021 | 104535). On the content around dosing and administration, additional tests for at-risk patients were given. The information on the page was written as 'baseline ECG [electrocardiogram] for patients with sinus bradycardia, a history of first or second degree AV [atrioventricular] block or history of myocardial infarction or heart failure'. The drug was actually contraindicated in the following sub-groups of patients (Section 4.3 of summary of product characteristics (SPC)): Patients who in the previous 6 months had a myocardial infarction (MI), unstable angina pectoris, stroke/transient ischaemic attack (TIA), decompensated heart failure (requiring inpatient treatment), or New York Heart Association (NYHA) class III/IV heart failure (Section 4.4) copy provided. Patients with a history of second-degree Mobitz type II AV block, third-degree AV block, sino-atrial heart block or sick-sinus syndrome, if they did not wear a pacemaker (Section 4.4). It was shocking that the page did not mention clearly that these groups of patients could not actually be given Mayzent. The additional test part should have made contraindications explicitly clear instead of providing test information for cardiac patients when these patients themselves should not be initiated on the product. Without providing the full information, a health professional could not make a rational choice and would be misled into thinking Mayzent was okay to use in a patient with myocardial infarction or heart failure, for example. The complainant alleged that a breach of Clause 6.1, 6.2, 5.1 and 2 had occurred as the contraindications information was not provided within the cardiac testing guidance.

The complainant stated that in small writing at the end of this section, there was mention that women of child-bearing potential were contra-indicated with Mayzent use. However, there were a number of other contraindications that were not provided here which included the following: Hypersensitivity to the active substance, or to peanut, soya or any of the excipients listed in Section 6.1 - Immunodeficiency syndrome. - History of progressive multifocal leukoencephalopathy or cryptococcal meningitis. - Active malignancies. - Severe liver impairment (Child-Pugh class C).

The complainant stated it was hugely misleading to only refer to pregnancy as the only contra-indication when there were a huge range of other contraindications. A busy health professional would only think pregnancy was the only single contra-indication which was not the case. The complainant alleged that Clause 6.1, 6.2, 5.1 and 2 had been breached. Novartis allegedly did not have a dedicated remote signatory team unlike other companies, which meant huge errors around compliance were happening and the constant restructuring of teams and lack of experienced signatories was detrimental to a safe compliance speak-up culture, according to the complainant.

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.

RESPONSE

Novartis stated that the complaint alleged that Novartis had made several breaches of the Code pertaining to the alleged promotion of its product, Mayzent.

As requested, in responding to the complaint, Novartis had borne in mind the requirements of Clauses 2, 5.1, 6.1 and 6.2 of the Code.

Background

Novartis stated that Mayzent (siponimod) was indicated for the treatment of adult patients with SPMS with active disease evidenced by relapses or imaging features of inflammatory activity. The anonymous complainant centred around a theme of insufficient information pertaining to contraindications. Novartis strongly refuted any such allegation, and for convenience, Novartis addressed the purported Code breaches in turn.

Clause 6.1

The complaint referenced Novartis' dosing and administration ('D&A') webpage and alleged the page failed to provide full information for health professionals, with particular regard to cardiac contraindications. There were a number of points Novartis wished to raise in responding to this allegation:

i) The website clearly displayed information in a logical sequence. The order of the information was relevant whereby health professionals could view the clinical and safety information first in order to inform their clinical decision to prescribe, then move onto the dosing and administration webpage, and beyond. The sequence of information, as seen on the side bar on the right-hand side of the webpage, was as follows (bold were of interest in this response; others were omitted for relevance):

    a. Clinical Data
        i. Efficacy
        ii. **Safety**
    b. [ ]
    c. **Dosing and Administration**
    d. [ ]
    e. [ ]
    f. [ ]
    g. Downloadable resources
        i. Resources for Healthcare professionals
        ii. **Risk Management Materials**
        iii. Resources for patients
    h. [ ].

ii) At this juncture it was important to note that the prescribing information (PI) was provided on every Mayzent webpage, including the webpage at the centre of the complaint. Access was attained via a PI link that appeared at the top of the content panel, for ease of access and reference. The linked Mayzent PI contained all information required according to Clause 12.2 of the Code, including but not limited to contraindications and additional monitoring requirements.

iii) The D&A webpage was specifically created to provide information around Mayzent and its initiation, administration, and ongoing monitoring. Further, links to the Efficacy and Safety pages could be accessed by clicking on Clinical Data, in addition to sections displayed at the bottom of the D&A webpage. With specific reference to the complaint, a full list of contraindications was displayed in the Mayzent Clinical Data Safety page . Finally, a full list of 'not-recommended' patients was also presented.

iv) The Risk Management Materials page provided a prescriber's checklist as part of Novartis' educational materials. Such material was designed as a checklist for prescribers to use when prescribing Mayzent and included contraindications and important points to remember prior to, during and post-treatment.

Novartis stated that the complaint implied that Novartis misrepresented or downplayed the risks associated with certain cardiac conditions. However, under 'Additional tests for at-risk patients', it was expressly stated to '[p]erform vitals and baseline ECG for patients with sinus bradycardia, a history of first- or second-degree AV block, or history of myocardial infarction or heart failure. Monitor these patients for 6-hour period after the first dose and obtain a second ECG at the end of the monitoring period'. This statement was indeed an accurate description of the requirement from the SPC for these at-risk patients (referenced at the bottom of the page). Novartis refuted any suggestion of misleading information or any other way that Mayzent could be used in a patient with myocardial infarction or heart failure.

Novartis stated that the complaint also took objection to the section about pregnancy, in particular, the section heading of 'Women of childbearing potential'. The aim of this section was to raise awareness of specific concerns during the treatment initiation phase from the SPC (referenced at the bottom of the page). The information presented in this section was a clear and accurate description of the SPC requirements for women of childbearing potential and it did not mislead a health professional to think that this was the only contraindication. The full list of contraindications was listed in the safety page.

Accordingly, Novartis fully refuted all allegations pertaining to a paucity of information regarding contraindications, and as such, no breach of Clause 6.1 of the Code.

Clause 6.2

Novartis stated that its response to an alleged breach of Clause 6.2 was the same as that set out above under Clause 6.1. In addition, and for completeness: (i) all information provided in the D&A webpage was taken from, and in line with, the Mayzent SPC and as such was capable of substantiation; and (ii) the webpage expressly provided a reference: MAYZENT (siponimod) Summary of Product Characteristics.

Accordingly, Novartis refuted the allegation that the information presented was not capable of substantiation, and as such, no breach of Clause 6.2 of the Code.

Clause 5.1

The Mayzent portal page was designed to provide product information within its license to UK health professionals in order to assist their understanding of the product's characteristics. This included clinical efficacy data, clinical safety data (including adverse events and contraindications), dosing and administration, patient support programme (MayzentConnect)

information, Mayzent patient cases, as well as downloadable materials (including RMP [risk management plan] materials). Further: (i) the PI was provided at the top of every page; (ii) all information presented is accurate, fair, balanced, referenced and capable of substantiation; (iii) references were provided on each page; and (iv) all webpages were certified according to the Code.

Accordingly, Novartis refuted any breach of Clause 5.1 because the company had maintained high standards at all times.

Clause 2

Regarding a potential breach of Clause 2, Novartis saw no evidence that its materials could bring discredit upon, or reduce confidence in, the pharmaceutical industry. Accordingly, Novartis did not accept a breach of Clause 2.

Culture

Novartis stated that as a final point, the complaint appeared to have concern around Novartis' compliance culture, with a particular focus on a lack or resourcing leading to 'huge errors around compliance' and that a 'lack of experienced signatories was [detrimental] to a safe compliance speak up culture'. It was interesting to note that the complainant made a blanket remark, but did not include any notion of context in time: Novartis purportedly 'did not have a dedicated remote signatory team', but when did this become an issue and for how long? Subsequently, there was reference to 'constant restructuring of teams', but nothing in terms of how this impacted compliance other than in the complainant's view it 'was [detrimental]'. The complaint, at least on this matter, was nothing but conjecture at best.

Novartis had a robust compliance process for all activities, requiring both legal and medical sign-off prior to review and certification by appropriately trained signatories from a Code perspective. Novartis took pride in its compliance culture and strongly refuted any suggestion of poor compliance, including, but not limited to, as a result of a paucity of or inappropriate signatories to relevant materials.

In summary, the complaint had raised a number of issues related to the advertising and promotion of Mayzent. Novartis believed that there was a legitimate defence to the alleged breaches of Clauses 2, 5.1, 6.1 and 6.2.

PANEL RULING

The Panel noted that the complaint was in relation to the promotion of Mayzent (siponimod) on the 'Dosing and administration' page on the www.health.novartis.co.uk website. The Panel noted the webpage at issue had a banner image at the top, beneath which was a hyperlink to prescribing information and four key sections: Initiation, Titration, Monitoring, Stopping. The complaint appeared to be in relation to the Initiation section.

The Panel noted the Initiation section included in large, capitalised font 'Starting patients on once-daily Mayzent follows a well-defined initiation protocol' and highlighted three key areas: 'Genotype testing', 'Blood test' and 'Skin examination'. Further down the webpage, beneath a dosing table, the highlighted box identified by the complainant was headed 'Additional tests for at risk patients' and referred to eye tests and ECG monitoring.

The Panel noted the section highlighted by the complainant read:

> **'Perform vitals and baseline ECG for** patients with sinus bradycardia, a history of first- or second-degree AV block, or a history of myocardial infarction or heart failure
>
> - Monitor these patients for a 6-hour period after the first dose and obtain a second ECG at the end of the monitoring period.'

Cardiac contraindications

The Panel noted the complainant's allegation that the initiation section should have made clear that Mayzent was contra-indicated in certain cardiac patients as listed in Section 4.3 of the SPC; the complainant alleged a health professional would be misled into thinking Mayzent could be used in patients with myocardial infarction or heart failure for example and the contraindications should have been provided within the guidance for cardiac testing.

The Panel noted that Section 4.3, Contraindications, listed 9 contraindications including:

> 'Patients who in the previous 6 months had a myocardial infarction (MI), unstable angina pectoris, stroke/transient ischaemic attack (TIA), decompensated heart failure (requiring inpatient treatment), or New York Heart Association (NYHA) class III/IV heart failure (see Section 4.4)
>
> Patients with a history of second-degree Mobitz type II atrioventricular (AV) block, third-degree AV block, sino-atrial heart block or sick-sinus syndrome, if they do not wear a pacemaker (see section 4.4).'

The Panel noted that Section 4.4 of the SPC, Special warnings and precautions for use, under 'Treatment initiation recommendation in patients with certain pre-existing cardiac conditions', stated:

> 'As a precautionary measure, patients with the following cardiac conditions should be observed for a period of 6 hours after the first dose of siponimod for signs and symptoms of bradycardia (see also section 4.3):
>
> - sinus bradycardia (heart rate <55 bpm),
> - history of first- or second-degree [Mobitz type I] AV block,
> - history of myocardial infarction, or
> - history of heart failure (patients with NYHA class I and II).
>
> In these patients, it is recommended that an electrocardiogram (ECG) is obtained prior to dosing and at the end of the observation period. If post-dose bradyarrhythmia or conduction-related symptoms occur or if ECG 6 hours post-dose shows new onset second-degree or higher AV block or QTc ≥500 msec, appropriate management should be initiated and observation continued until the symptoms/findings have resolved. If pharmacological treatment is required, monitoring should be continued overnight and 6-hour monitoring should be repeated after the second dose.'

The Panel noted Novartis' submission that the dosing and administration webpage was created to provide information around Mayzent's initiation, administration, and ongoing monitoring and

that further links to the Efficacy and Safety pages could be accessed from the webpage at issue; a full list of contraindications and not-recommended patients was displayed on the safety page and the prescriber's checklist on the Risk Management Materials page included contraindications and important points to remember prior to, during and post-treatment. Novartis also stated that the prescribing information was provided on each webpage. The Panel considered that each webpage should be capable of standing alone in relation to the requirements of the Code.

The Panel noted the treatment initiation recommendation under Section 4.4 of the SPC referred readers to important safety information contraindications under Section 4.3.

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.

In the Panel's view, the dosing and administration webpage for Mayzent did not necessarily need to list all of its contraindications. However, the Panel considered that by referring to Mayzent initiation in patients with a history of myocardial infarction or heart failure without referring to the absolute contra-indication in patients with a history of myocardial infarction or heart failure in the previous 6 months, meant that a health professional would, on balance, think that Mayzent was suitable to use in patients with a 6-month history of these conditions which was not so. In the Panel's view, the inclusion of the relevant contraindications on a separate webpage or within the prescribing information was insufficient to negate the immediate misleading impression. The Panel considered the material misleading as alleged on this point and ruled a **breach of Clause 6.1.**

The Panel noted the reasons for its ruling of a breach of Clause 6.1 set out above. The Panel considered that the misleading impression that Mayzent was suitable to use in patients with a 6-month history of myocardial infarction or heart failure was not capable of substantiation and ruled **a breach of Clause 6.2** accordingly.

The Panel noted its comments and ruling of a breach of Clauses 6.1 and 6.2 above and considered that Novartis had failed to maintain high standards and **a breach of Clause 5.1** was ruled.

The supplementary information to Clause 2 listed prejudicing patient safety as an activity likely to lead to a breach of this clause. The Panel was concerned that providing information on initiating patients with a history of myocardial infarction or heart failure, without mentioning that Mayzent was contraindicated in patients who, in the previous 6 months, had a myocardial infarction, decompensated heart failure (requiring inpatient treatment), or NYHA class III/IV heart failure meant that there was a risk that some readers might consider that such patients could be treated with Mayzent, which was not so. The Panel considered the inclusion of this information on separate webpages, was insufficient in this regard and did not negate the misleading immediate impression given that Mayzent could be initiated in any patient with a recent history of MI or heart failure. Patient safety was of the utmost importance and the Panel considered that the omission of such important information might potentially prejudice patient safety and was such as to reduce confidence in, and bring discredit upon, the pharmaceutical industry. **A breach of Clause 2** was ruled.

Pregnancy section

The Panel noted that on the webpage in question directly beneath the section 'Additional tests for at-risk patients' described above, was information on pregnancy and breastfeeding:

> '**Women of childbearing potential**
> Due to risk for the foetus, siponimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. Before initiation of treatment, women of childbearing potential must be informed of this risk to the foetus, must have a negative pregnancy test and must use effective contraception during treatment and for at least 10 days after treatment discontinuation. MAYZENT should not be used during breastfeeding.'

The Panel noted the allegation that it was misleading to only refer to pregnancy when there were a huge range of other contraindications and that a busy health professional would be misled into thinking that pregnancy was the only contra-indication.

The Panel noted Section 4.3, Contraindications, listed additional contraindications including hypersensitivities, immunodeficiency syndrome, history of progressive multifocal leukoencephalopathy or cryptococcal meningitis, severe liver impairment (Child-Pugh class C) and patients homozygous for CYP2C9*3 (CYP2C9*3*3) genotype (poor metaboliser), besides those relevant for patients with a history of cardiac conditions outlined above.

The Panel did not consider that in highlighting the contraindication in pregnancy for a medicine licensed to treat certain adult patients with secondary progressive multiple sclerosis meant that health professionals would assume there would be no other considerations or contraindications. The Panel ruled **no breach of Clause 6.1** in this regard.

The Panel considered that the complainant had not established that the material was not capable of substantiation and **no breach of Clause 6.2** was ruled.

The Panel noted its rulings of no breaches in this regard and ruled **no breach of Clause 5.1 and Clause 2** accordingly.

Complaint received **6 June 2022**

Case completed **27 June 2023**