Medicines Australia

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COMPLAINT OUTCOME

1179 - Promotional material related to REPATHA

DETERMINATIONS OF THE MEDICINES AUSTRALIA CODE OF CONDUCT AND APPEALS COMMITTEES

The administration of the Code is supervised by the Code of Conduct Committee. The Code of Conduct Committee has the power to make a determination as to a breach of the Code and impose sanctions. The right of appeal is available to both the Complainant and Subject Company. An appeal is heard by the Appeals Committee which has the power to confirm or overturn the decision and to amend or remove any sanctions.

The decisions of the Code of Conduct and Appeals Committees are relevant to the date of publication of the materials subject to complaint and approved Product Information (PI) at that time. A complaint is not deemed finalised until both parties have advised Medicines Australia that they will not appeal the outcome of the Code of Conduct Committee decision (following circulation of the Committee's Reasons) or, in the case of an appeal, the Appeals Committee Reasons have been provided to both parties.

This report is an extract of the minutes of the complaint heard by the Code Committee on 18 August 2025 and an extract of the minutes of the appeal heard by the Appeals Committee on 17 October 2025.

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Medicines Australia

COMPLAINT 1179 Promotional material related to REPATHA

SUBJECT COMPANY	PRODUCT	COMPLAINANT
Amgen	REPATHA (evolocumab)	Novartis

COMPLAINT

Novartis alleged that Amgen engaged in multiple breaches of the Code through the promotion of Repatha. The complaint concerned two promotional items directed at healthcare professionals, one being a *Medical Republic* article and the other a *Medicines Today* Electronic Direct Mail (EDM) (**'the materials'**). It focused on three aspects of these materials:

1. that a Product Information Table showing comparative information was misleading;
2. that comparisons that were presented as being based on three network meta-analyses (NMAs) were misleading; and,
3. that comparative claims based on ORION-3 data were also misleading ('**key issues**').

For context, the materials promote Amgen's Repatha (evolocumab) and included comparisons with inclisiran, the active ingredient in Novartis's Leqvio. Both evolocumab and inclisiran are injectable treatments for high cholesterol, that work by specifically lowering low density lipoprotein cholesterol (LDL-C) levels.

SECTIONS OF THE CODE (EDITION 20)

- Overarching Principle 3: Companies are responsible for providing current, accurate, balanced, and scientifically valid information products to support their use.
- Overarching Principle 7: Information relevant to prescribing, in particular product and safety information, are clearly communicated in all promotional materials. Promotional materials are designed by Companies to not only create awareness of Therapeutic Goods Administration (TGA) approved medicines, but to support proper assessment of their risks and benefits.
- Section 1.2: Substantiating Data

RESPONSE TO THE COMPLAINT

Amgen denied the materials breach the Code and asserted all claims that were made in the materials were "supported by adequate levels of clinical evidence and are consistent with the approved Product Information for each of the products mentioned in the materials".

In their response, Amgen outlined the complaint's history through the ICD process and alleged that Novartis expanded the scope of the original complaint. Amgen also claimed that one issue had been resolved, while others have been newly introduced without undergoing ICD. On this basis, Amgen requested that the Committee refrain from adjudicating multiple aspects of the complaint. This position shaped their response and led to a counter complaint, where they alleged that Novartis breached **Section 15.5 of the Code,** titled 'Failure to follow Intercompany Dialogue Standards'. Nonetheless, Amgen provided a defence on all matters, should the Committee have decided to adjudicate the "new allegations."

CODE COMMITTEE DECISIONS

The Code Committee considered the complaint and determined there were breaches of the Code. Sanctions were applied by the Code Committee. See the table of Committee Decisions below, and the Code Committee Reasons on pages 4-7. The Code Committee also considered the counter-complaint and determined that the subject company did not breach Section 15.5 - 'Failure to follow Intercompany Dialogue Standards.' See the Code Committee Reasons on page 8-9.

APPEAL

The subject company appealed part of the findings of the Code Committee. The findings in relation to Section 1.2 and the counter complaint (that the complainant had not breached the ICD Standards) were not appealed, nor were the findings in relation to the Product information Table (set out in page 4). However, the subject company appealed the remaining Code Committee decisions, including the breach classification (moderate) and the resulting penalty. The complainant did not appeal any findings of the Code Committee but did provide a response to the subject company's appeal.

APPEAL COMMITTEE DECISIONS

The Appeals Committee upheld all findings of the Code Committee, reconfirming breaches of the Code. The sanctions were upheld. The Reasons for their Decisions are on pages 9-14.

Summary of Decisions

	Principle 3	Principle 7	Section 1.2	Code Committee Sanctions	Appeals Committee Sanctions
Product Information Table				• $130,000 fine (moderate breach). • Withdrawal of materials found in breach (where they are still in circulation) as well as any other promotional material containing the claims found in breach. • The content found in breach must not be used in the same or similar form.	• Code Committee decision upheld • Due to the decisions of the Code Committee being upheld in their entirety, Medicines Australia will retain Appeal bond.
Code Committee	**Breach** (Unanimous)	**Breach** (Unanimous)	(d) **No breach** (unanimous) (k) **No breach** (unanimous)		
Appeals Committee	Not appealed	Not appealed	Not appealed		
Network Meta-Analyses					
Code Committee	**Breach** (Unanimous)	**Breach** (Unanimous)	(a) **No breach** (unanimous) (d) **No breach** (majority) (k) **No finding** (majority)*		
Appeals Committee	**Breach** (Unanimous)	**Breach** (Unanimous)	Not appealed		
ORION-3					
Code Committee	**Breach** (Unanimous)	**Breach** (Unanimous)	(d) **No breach** (unanimous) (k) **No breach** (majority)		
Appeals Committee	**Breach** (Unanimous)	**Breach** (Unanimous)	Not appealed		

**This specific issue appeared to have been resolved by agreement during the ICD. Therefore, the Committee did not make a formal determination on this point in its final decision.*

SUBJECT COMPANY REQUEST

In its response, the subject company requested that the Committee refrain from considering certain allegations raised by the complainant, specifically those that:

(a) were not included in the Formal Written Complaint (the initial written communication from the complainant to the subject company that initiated the ICD process, as defined in the ICD Standards), and
(b) were allegedly resolved during the Intercompany Dialogue (ICD).

In determining how to proceed, the Committee considered the following:

- The Committee referred to **Clause 15.1(c)** of the Code, which states: *"Medicines Australia will not accept a complaint from a Company unless it has been clearly demonstrated that intercompany dialogue has taken place and the complaint has not been resolved."*
- Based on this provision, the Committee concluded that it had the authority to adjudicate a complaint, and components of a complaint, provided that ICD had occurred. The adequacy of the ICD process, and whether specific elements were included in the Formal Written Complaint, or at what stage they were raised in the ICD process, should be assessed under the counter allegation of a breach of Clause 15.5.
- The Committee further acknowledged, consistent with the approach taken by previous Committees, that the Code does not prevent it from adjudicating a matter because one party wishes to proceed while the other does not. In relation to the subject company's assertion that one element of the complaint had already been resolved, the Committee found that resolution had not been achieved to the satisfaction of both parties. Accordingly, it was deemed appropriate for the Committee to consider this aspect of the complaint.
- The Committee then turned its attention to whether **Intercompany Dialogue (ICD)** had occurred on the key issues raised in the complaint, particularly in light of the subject company's request that those matters not be adjudicated.
- The Committee noted that the subject company had documented intercompany discussions on all three of the key issues during ICD and was therefore satisfied that ICD had taken place on those issues.
- While each key issue had been broken down into multiple sub-elements by the complainant, the Committee decided to adjudicate the overarching key issues as presented in the materials, rather than addressing each sub-element individually. The sub-elements were regarded as a detailed explanation of the broader concerns, rather than new or separate issues.
- In making this determination, the Committee recognised that ICD is an interactive process designed to explore and resolve concerns, and that issues may naturally evolve or be clarified in the course of such dialogue. The Committee acknowledged that this organic development should not preclude adjudication simply because additional detail or explanation emerged during ICD, nor should it trigger a new ICD process, provided that newly emerging detail relates to the underlying concerns that formed the basis of the Formal Written Complaint.
- Moreover, the Committee considered it was not appropriate or necessary to undertake an overly detailed assessment of the ICD process in determining which aspects of the complaint could be considered. The Committee was satisfied that, where the substance of a complaint is clear, and there has not been a resolution through ICD that is satisfactory to both parties, the Committee should ordinarily take into account all aspects relevant to the substance of the complaint for which no resolution has been reached, rather than limit its consideration through a narrowly procedural review of the ICD material.
- **Accordingly, the Committee was satisfied that the three key issues had been the subject of ICD, and that the specific elements raised in the complaint could reasonably be regarded as relevant elaborations of those original concerns.** On this basis, the Committee proceeded to consider the substance of the complaint.

CONSIDERATION OF THE COMPLAINT by the CODE COMMITTEE

Concern 1 – Product Information Table ('the table')

- The Product Information Table was substantially the same in both advertisements. It was headed "*Monoclonal antibodies have a positive effect on LDL-C lowering, CV outcomes and plaque modification, with established safety data*", and used green ticks and red crosses that indicated whether three properties (LDL-C lowering, cardiovascular outcomes, and modification of coronary plaque properties) were applicable to each of three medicines (Repatha, alirocumab, and inclisiran). There were two red crosses in the table, both in relation to cardiovascular outcomes and modification of coronary plaque properties for inclisiran. Smaller text under the table stated that "there are no head-to-head data available comparing the efficacy or safety of Repatha, alirocumab, and inclisiran."
- The Committee considered Novartis's allegation, originally framed in its Formal Written Complaint as: "*The table depicted is potentially misleading to prescribers as it unfairly misrepresents the risk and benefit profile of Repatha versus inclisiran.*" Following ICD, the subject company had removed the tick-cross table from some versions and addressed concerns regarding time periods applicable to safety data presented in the table.
- The Committee was satisfied that the Product Information Table in the advertisements clearly constituted a comparison between Repatha and inclisiran. Given this interpretation, the Committee highlighted the need for comparative material to be presented in a fair and just manner, and extra care needs to be taken to ensure that any comparison properly reflects the body of evidence and does not mislead by distortion, by undue emphasis, or in any other way.
- Given the absence of head-to-head data to substantiate the comparison, the Committee considered the subject company's decision to present this information in a comparative table to warrant a higher standard of diligence - particularly in avoiding claims that could be misleading or carry undue emphasis.
- The Committee was satisfied that the table, in its total context, conveyed that there was appropriate evidence to demonstrate that Repatha would have benefits in relation to cardiovascular outcomes and modification of coronary plaque properties.
- However, the Committee was also satisfied that the table, in its total context, conveyed unsupported claims about inclisiran's lack of cardiovascular benefits and effects on coronary plaque. It was submitted that the red crosses were a visual representation intended to indicate a lack of evidence for inclisiran on those criteria; however, the Committee considered that their bold presentation, combined with the table's comparative format, would likely lead a reasonable viewer to conclude that inclisiran had been shown to offer no such benefits. As no data exists to support this impression, and this was not made clear, the presentation was considered misleading.
- The Committee noted that, if the intention of the table had been to convey that there was insufficient data in relation to inclisiran and cardiovascular outcomes and modification of coronary plaque properties, then a more appropriate symbol than a cross could have been selected, such as "*not applicable* or '*N/A*'," "*no data available*," or even an asterisk with an accompanying explanation.
- In considering the overall impression and impact of the table, the Committee considered that the title, '*Monoclonal antibodies have a positive effect on …*', did not serve as a neutral descriptor of the data but instead constituted a promotional claim, priming the reader's interpretation of the table. The Committee concluded that the table conveyed a misleading impression of product superiority, primarily through the use of bold visual elements such as green ticks and red crosses but also taking into account the overall context. Although Amgen included a disclaimer noting the absence of head-to-head data between Repatha and inclisiran, the Committee found it insufficient to counteract the overall misleading message.
- On that basis, **the Committee determined the table breached Overarching Principle 3** because it did not provide accurate, balanced, and scientifically valid information about the products in the table to support their appropriate use.

Concern 1 – Product Information Table ('the table') continued

- **The Committee also determined that the table breached Overarching Principle 7** as it did not support the making of a proper assessment of the products' risks and benefits.
- The Committee determined that, although the table reflected some selective use of data, it did not present "consistent positive results while neglecting consistent negative results from a systematic review or meta-analysis…". **Accordingly, the allegation that the table breached Section 1.2(d) was not substantiated, and no breach was found.**
- The Committee determined that the table did not include data that was not statistically significant. **Accordingly, the allegation that the table breached Section 1.2(k) was not substantiated, and no breach was found.**

Concern 2 – Use of Network Meta-Analyses (NMAs)

- The materials each included a section headed "*Repatha has demonstrated consistently greater reductions in LDL-C than inclisiran in a series of meta-analyses*", and referred to three network meta-analyses: Toth et al, Burnett et al, and Huang et al.
- The Committee considered the claim Repatha achieves "*consistently greater reductions in LDL-C than inclisiran*" and Novartis' corresponding allegation, originally framed in its Formal Written Complaint as: "*Using an NMA as a basis for promotional claims can be misleading, as the indirect nature of the comparisons does not provide the definitive evidence required to claim superiority*", thereby rendering the information misleading.
- The Committee acknowledged that, consistent with Medicines Australia's Guidance, meta-analyses (including network meta-analyses) may be used to combine and analyse the results of several studies. Indeed, it was the view of the Committee that network meta-analyses can be valuable. However, the Committee noted that there are inherent limitations to network meta-analyses, and they are not usually regarded as the highest level of evidence.
- As comparative claims should reflect the full body of evidence and be based on the highest available level of evidence, the Committee determined that the reliance on the cited network meta-analyses and the manner in which the results were described was inappropriate in this case. Their inherent limitations and insufficient statistical power meant they could not properly support the strength of the comparative claim made.
- The Committee further observed that the materials at times referred to the cited studies simply as "*meta-analyses*" rather than "*network meta-analyses.*" While a network meta-analysis is a type of meta-analysis, the term "meta-analysis" generally implies direct comparison of treatments, and the omission of "network" obscured the indirect nature of the evidence and risked misleading healthcare professionals into believing direct comparative data existed when it did not.
- The Committee noted that the materials did acknowledge the limitations of the network meta-analyses, and in a more comprehensive manner than seen in some past cases. However, the presentation of the data, through illustrative graphs and a promotional claim, conveyed a stronger impression of certainty than the evidence could support. The Committee considered that the stated limitations were insufficient to offset this impression, given the level of evidence.
- The Committee also noted that while the Toth and Huang network meta-analyses reported statistically significant differences favouring Repatha, the materials also cited Burnett et al., whose findings were not statistically significant and described inclisiran as having comparable, not lesser, efficacy. Accordingly, the Committee determined that the claim of "consistently greater reductions" was misleading, as it was not accurate in light of the total body of evidence and conveyed a greater degree of consistency and superiority than the data could support.

Concern 2 – Use of Network Meta-Analyses (NMAs) continued

- On this basis, the Committee found that the use of the three network meta-analyses in the manner employed contributed to a claim that did not uphold the principles of accuracy or balance and failed to support proper assessment of the product's risks and benefits. **The Committee therefore determined that this constituted a breach of Overarching Principles 3 and 7.**
- The Committee determined the substantiating data did not consist solely of unpublished data, so it did not fall within the scope of section 1.2(a) of the Code. **Accordingly, there was no breach of Section 1.2(a).**
- The Committee determined that the data did not report negative results; rather, two network meta-analyses showed positive findings, and one was neutral. Therefore, the allegation that the use of network meta-analyses reflected "*consistent positive results while neglecting consistent negative results from a systematic review or meta-analysis…*" was unfounded. **Accordingly, the material did not fall within the scope of Section 1.2(d) of the Code and there was no breach of this provision.**
- The Committee acknowledged that Amgen subsequently rectified the issue by removing the reference to the Burnett study and understood that this was accepted by Novartis as a resolution to that particular aspect of the complaint.
- The Committee noted, as acknowledged by Amgen, that the Burnett findings were not statistically significant. As the material did not include a qualifying statement to this effect, the Committee considered that this omission would ordinarily constitute a breach of Section 1.2(k) of the Code. However, as this specific issue appeared to have been resolved by agreement during the ICD, **the Committee did not make a formal determination on this point in its final decision.**

Concern 3 – Use of ORION-3

- The material relating to ORION-3 included the words, "*While there are no head-to-head data available comparing the efficacy or safety of Repatha and inclisiran, we can gain some additional insight from the ORION-3 trial*". It included a prominent side-by-side graphic showing three different rates of LDL-C reduction, namely:

  (i) "61%… with Repatha… Year 1";
  (ii) "45%… with inclisiran… Years 2-4"; and,
  (iii) "44 %… with inclisiran… Years 1-4".

- The 61% graphic was brightly coloured, while the 45% and 44% graphics were grey.
- The Committee considered that ORION-3 was an exploratory, open-label extension of a Phase 2 dose ranging trial (ORION-1), designed to assess the long-term safety and efficacy of inclisiran. There were no randomised, controlled, or blinded comparator arms. The resulting analysis for comparison purposes was limited.
- There were two arms to the study:

  (i) One arm (**the inclisiran-only arm**) was effectively a continuation of the active arms from a previous study; subjects in this arm were administered inclisiran six-monthly for four years and had already been administered inclisiran for the period of the prior ORION-1 study.
  (ii) The second arm (**the "switching" arm**) was drawn from the placebo arms of the previous study. Patients in this arm were treatment-naïve and were administered evolocumab fortnightly for one year, and then inclisiran six-monthly for the remaining three years of the ORION-3 study.

Concern 3 – Use of ORION-3 continued

- It was not, in the Committee's view, appropriate or accurate to place the three different rates of LDL-C reduction side-by-side when they related to subject groups that were significantly different (a treatment-naïve group vs a group that had been treated during the previous study), and where the time periods (year 1, years 2-4, years 1-4) were different.
- Fundamentally, the ORION-3 study may be of clinical interest, but it was not a head-to-head comparison between Repatha and inclisiran, nor was it designed or powered for outcomes to be presented in the way that they were.
- In the Committee's view, any reasonable reader of the advertisements would likely regard the rates of LDL-C reduction presented in the graphic as a valid and direct comparison of the efficacy of Repatha as compared with the efficacy of inclisiran. The ORION-3 study was not an appropriate evidentiary basis for such a comparison. The Committee noted that the data must be communicated with care, and that utmost diligence should be exercised when using it in promotional material.
- As noted, the Committee emphasised that comparative material must be presented fairly and accurately, reflecting the full body of evidence without distortion or undue emphasis. In this case, the infographic displayed three side-by-side statistics derived from data that should not have been conflated, creating an impression of Repatha's superiority over inclisiran that was not supported by the available body of evidence.
- Although Amgen included a clear footnote stating the absence of head-to-head data *("there are no head-to-head data available comparing the efficacy or safety of Repatha and inclisiran",)* and the exploratory nature of the endpoints, the Committee found that such footnotes could not correct the primary message communicated by the presentation of the ORION-3 data.
- Overall, the Committee found that the ORION-3 data was not presented fairly or accurately. The comparisons spanned different time points, treatment stages, and prior treatment exposures, making them inappropriate for side-by-side comparison in the manner presented. The result was misleading and failed to support proper assessment of the product's risks and benefits. **The Committee therefore determined that this constituted a breach of Overarching Principles 3 and 7.**
- The Committee determined that the ORION-3 data did not report "*consistent positive results while neglecting consistent negative results…*". **Accordingly, there was no breach of Section 1.2(d)**.
- Whilst the promotional material invited comparisons to be made from ORION-3, the Committee considered that ORION-3 was not designed or powered for efficacy comparisons between products. Accordingly, the material did not fall within the scope Section 1.2(k) of the Code and **there was no breach of this provision.**

Sanctions

- The Committee determined the materials had no significant safety implications to patient wellbeing but would be likely to have a moderate effect on how the medical profession will prescribe the product. For these reasons, the Committee was satisfied the breaches arising from the materials should be categorised as moderate.
- The Committee considered what sanctions were appropriate, having regard to the following factors:

  (i) Whether the breach should have been clearly evident to the subject company;
  (ii) Length of time that the materials have been in use;
  (iii) The number and type of alleged breach/es;
  (iv) Circumstances in which the activity took place – and whether any explanation was offered by the subject company;
  (v) Whether a subject company engaged in ICD in good faith;
  (vi) Whether a subject company made reasonable concessions in response to ICD or the complaint itself; and
  (vii) Where prescribing behaviour may be affected, the likely degree of the effect.

CONSIDERATION OF THE COMPLAINT by the CODE COMMITTEE (continued)

Sanctions

- The Committee considered the breaches should have been evident to the subject company. The materials were clearly comparative, and extra care should have been taken to ensure that those presented comparisons did not mislead by distortion, by undue emphasis or in any other way.
- The Committee considered that the ICD was conducted in good faith, with the subject company making reasonable concessions, albeit incomplete for resolution, during the process.
- The Committee determined that a fine was appropriate, and this be at the mid-upper fine threshold associated with a moderate breach.
- The Committee imposed the following sanctions:

    (i) Single monetary fine of $130,000.
    (ii) Withdrawal of the materials found in breach (where they are still in circulation) as well as any other promotional material containing the claims found in breach
    (iii) The content found in breach must not be used in the same or similar form.

- The Committee did not impose corrective action, determining that a monetary fine coupled with the withdrawal and cessation would be adequate.

FAILURE TO FOLLOW ICD STANDARDS - ALLEGATION

The subject company alleged that the complainant breached Section 15.5 of the Code, titled **'Failure to follow Intercompany Dialogue Standards**'. This allegation was supported by a rationale that was interwoven throughout the subject company's detailed submission. The primary basis of the complaint was the subject company's view that the complainant introduced additional information during the Intercompany Dialogue (ICD) meeting and in subsequent correspondence, rather than clearly presenting it in the initial written complaint. The subject company also raised supplementary concerns to reinforce its position.

In its determination of this allegation, the Committee noted the following:

- It was considered that, notwithstanding the counter-complaint and grievances raised, the ICD process was conducted in a reasonably respectful and constructive manner, with both parties engaging in good faith. This was demonstrated by the resolution of at least one issue without Committee involvement, indicating that the process was overall reasonable.
- The Committee noted that while Amgen raised concerns about the duration of the ICD process, responsibility for meeting the timeframe does not rest solely with the initiating party. Although Novartis commenced ICD, both companies actively participated in the dialogue, and the extended timeline appeared to reflect mutual engagement rather than deliberate delay. The ICD Standards also allow for flexibility in timing when mutually agreed, and the Committee did not consider that Novartis had intentionally prolonged the process.
- The Committee noted that although the subject company had offered to amend its materials in response to the concerns raised, the matter remained unresolved. The Committee commended the company's willingness to make concessions but observed that such steps are a normal and constructive part of the ICD process and may not fully resolve a complainant's concerns. As this matter demonstrated, concessions do not automatically conclude a complaint, and where one party remains aggrieved, the complaint may properly continue.

FAILURE TO FOLLOW ICD STANDARDS - ALLEGATION continued

- The Committee noted the subject company's concerns that the complainant may have broadened the scope of the complaint beyond what was outlined in the Formal Written Complaint. Under the ICD Standards, companies are expected to be specific and comprehensive in their written communications, and the Formal Written Complaint defines the scope of ICD. New elements or materials not included in the initial Formal Written Complaint should not be introduced during the process.
- However, the Committee considered that, although the final complaint included more detail than the original, it remained aligned with the broader concerns initially raised. The additional arguments were viewed not as new or separate issues, but as reasonable elaborations of the original complaint - likely clarified through the ICD process.
- That said, the Committee noted that Novartis could have been more specific and comprehensive in its Formal Written Complaint, in line with the intent of the ICD Standards. The Committee was also concerned to observe that Novartis referenced clauses 1.3, 2.3, and 10.2 in one of the letters in ICD - clauses which did not correlate with their concerns and did not seem to correspond with appropriate Code sections.
- However, the lack of detail did not warrant a breach, and on balance, the Committee found **no breach of Section 15.5**, as the Intercompany Dialogue Standards had been appropriately followed by Novartis.

CONSIDERATION OF THE COMPLAINT by the APPEALS COMMITTEE

The Appeal Material and Process

- The subject company appealed four of the nine findings of the Code Committee in relation to **Concern 2 - Use of Network Meta-Analyses** and **Concern 3 - Use of ORION-3.** The subject company did not appeal any of the findings in relation to **Concern 1 - Product Information Table.** The areas of appeal can be found on the Summary of Decisions Table on page 3 of this document.
- The complainant did not appeal any findings of the Code Committee but submitted that the appeal should be dismissed and the sanctions maintained. The complainant further considered that the Code Committee's decision aligned with the expected standards for promotional materials and that its reasons appropriately explained how the comparative claims conveyed a greater level of certainty and superiority than the evidence supported, notwithstanding the inclusion of disclaimers.
- Section 15.7 of the Medicines Australia Code of Conduct provides that an appeal is a rehearing of the original complaint and that the Appeals Committee may affirm, set aside, or vary findings and/or sanctions of the Code Committee, provided that the Appeals Committee is "persuaded that the findings of the Code Committee, or the sanction imposed by it, involved an error on the basis of which they should be set aside or varied".
- The Appeals Committee (hereafter referred to as '**the Committee**') noted that the subject company had requested clarification on several of the reasons for decision and had respectfully disagreed with the approach taken by the Code Committee in (the subject company submitted) deciding not to adjudicate on each individual sub-element of the arguments put forward. The Committee clarified that its remit is confined to the responsibilities outlined in Section 15.7 and does not extend to commenting on the adjudication approach adopted by the Code Committee, save where that approach demonstrates an error of the type identified above.

The Appeal Material and Process (continued)

- In that context, the Committee acknowledged the subject company's concern that the Code Committee had focused on 'overarching' issues rather than addressing each sub-element of the complaint individually. As noted above, while the Appeals Committee does not comment on the adjudication method itself, it did not consider there to be an error arising from the Code Committee's Reasons. That paragraph addressed overarching issues relating to the ICD process — a matter not the subject of the present appeal.
- The Committee was satisfied that it was appropriate, in determining the appeal, to consider the following material:

    (i) the original complaint materials from the complainant;
    (ii) the original complaint materials from the subject company;
    (iii) the appeal material submitted by the subject company;
    (iv) the appeal material submitted by the complainant;
    (v) the oral submissions on behalf of the subject company and the complainant, including their responses to questions posed by members of the Committee; and
    (vi) the Code Committee's reasons.

The findings in relation to the use of Network Meta Analysis ('NMAs')

- The materials each included a section headed "*Repatha has demonstrated consistently greater reductions in LDL-C than inclisiran in a series of meta-analyses*", and referred to three network meta-analyses (NMAs): Toth et al, Burnett et al, and Huang et al. The Committee considered that this was the headline claim in issue and noted that it appeared in bold text early on in the promotional materials.
- The Committee affirmed the decision made by the Code Committee, being that the use of the three NMAs in the manner employed contributed to a claim that did not uphold the principles of accuracy or balance because they overstated the comparative efficacy. In doing so, the claim failed to support proper assessment of the product's risks and benefits. **The Appeals Committee unanimously determined that this constituted a breach of Overarching Principles 3 and 7.**
- The Committee acknowledged that Toth is likely the most comprehensive NMA comparing the efficacy of non-statin therapies added to maximally tolerated statins as it considers a greater number of studies than others (including a greater number of data points relating to each of evolocumab and inclisiran). Furthermore, neither the complainant nor the Appeals Committee suggested that the findings of Toth are inaccurate nor suggested Toth was inconsistent with, or a departure from, the body of evidence.
- However, the Committee considered that the inherent limitations of NMAs mean that they cannot be afforded the same weight as randomised controlled head-to-head trials or pairwise meta-analyses (MAs). Accordingly, Toth - like any NMA - could not substantiate the strength of the comparative claim as it was specifically presented in the subject company's promotional materials. While Toth may represent the best available evidence in the absence of head-to-head trials, this does not elevate it to the evidentiary strength of such trials or justify drawing a strong comparative claim as present in the promotional materials. The Committee considered that all evidence, including the best available, must be used responsibly and in proportion to its limitations; in this case, the claim was too assertive given the indirect nature of the comparative analysis.
- The Committee also noted that NMAs represent a lower level of evidence than well-conducted, randomised controlled trials or pairwise MAs because they rely on indirect data and therefore inherit the limitations and biases of the included studies. In particular NMAs, including Toth, depend on assumptions of comparability and consistency across trials (e.g. patient populations, endpoints, and designs). While they can provide valuable indirect evidence, they are unlikely to adequately support definitive or strong comparative claims, as demonstrated through this complaint.

The findings in relation to the use of Network Meta Analysis ('NMAs') (continued)

- The Committee observed that NMAs are most commonly used in regulatory assessment, health technology assessment (HTA), and economic modelling rather than in day-to-day clinical prescribing. As a result, many healthcare professionals may not be familiar with NMAs or other forms of indirect comparison analyses. Owing to their indirect nature and limitations, they are less suited to guiding individual treatment decisions and are regarded as supportive evidence rather than definitive proof. This context further highlights their limitations in adequately supporting strong headline or definitive comparative claims, such as the one in this case.
- The Committee also considered that:
  (i) the subject company's promotional materials contained several references to 'meta-analyses' that did not include the word 'network'. Those statements were incorrect as Toth, Burnett and Huang et al were not MAs. The Committee considered that that omission suggested that the supporting evidence being cited in the promotional material was stronger than it actually was. The Committee noted that the subject company had agreed to correct those statements, but that the material had already been published in the original form;
  (ii) the use of the word 'series' in the headline claim, when describing the NMAs, suggested more than two NMAs but the Burnett et al NMA did not indicate statistically significant reductions. The Committee considers that two is not a series;
  (iii) although the subject company had included disclaimers and explanations in the body of the promotional material, the strength and prominence of the claim was such that those disclaimers and explanations were not sufficient to dispel the issues with the claim discussed above. The Committee agreed with the complainant that it was appropriate to consider the overall impression conveyed by the promotional material. In this regard, while the claim must be assessed in context, that context includes factors such as the claim's location, prominence, emphasis, and positioning within the material.
- The Committee did not agree that the Code Committee's reasoning prevented the subject company from using Toth to potentially support other promotional claims for Repatha. While recognising the practical challenges of relying on any material, study or source related to a previously determined breach, the Committee affirmed that the finding concerned the presentation of the current comparative claim, which overstated the certainty of the evidence, not the validity or usefulness of Toth itself.
- The Committee noted that the subject company had suggested the decision of the Code Committee was inconsistent with Medicines Australia Guidance and did not agree. The Medicines Australia Guidance refers to the use of MAs, not NMAs, and at no time did the Code Committee suggest that MAs (or NMAs) could not be used to support a promotional claim, only that the strength and certainty of the claim in issue was not supported by the materials cited.
- Nonetheless, in light of the concerns raised by the subject company, the Committee recommended that Medicines Australia incorporate detail into the Guidance to provide greater clarity for industry with respect to the use of NMAs and other types of indirect analyses. The Guidance could confirm that while indirect analysis such as NMAs have a place in evidentiary considerations of a product, such analyses alone are unlikely to substantiate strong comparative claims, particularly in the absence of direct randomised, placebo controlled, head-to-head trial data. The Committee also considered that, where NMAs or other types of data analysis that HCPs are likely to be less familiar with, are being used to support claims in promotional materials, it may be helpful to include a clear explanation on that type of analysis to assist the HCP in understand where it sits within the hierarchy of evidence.

The findings in relation to the use of Network Meta Analysis ('NMAs') (continued)

- It was also noted during Committee discussions that Toth received industry funding, although this was not disclosed in the materials. While this issue was not raised in the appeal and did not form the basis of any of the Committee's findings set out above, the Committee acknowledged that transparency regarding study funding and sponsorship is important for supporting informed interpretation of evidence, and this could be identified in promotional materials. The Committee noted there may be merit in Medicines Australia considering whether future guidance could further clarify expectations regarding disclosure where a NMA is industry funded.
- In line with the Code Committee's reasoning, the Appeals Committee acknowledged that the materials outlined several limitations of the NMAs - generally consistent with those cited in the publication.
- Irrespective of the limitations used, the Committee determined they were not sufficient in light of the strength of the claim (which appeared as a bold header in the promotional materials). Further, whilst the Guidance makes clear that NMAs may be used where their limitations are disclosed, the inclusion of these limitations does not counteract or justify making a claim that overstates the strength of the evidence ('*fine print cannot cleanse a misleading primary message*'- as per the complainant's view).
- The Committee considered that, under the Code and its Guidance, the primary obligation is to ensure that claims are accurate, scientifically valid, and appropriately substantiated from the outset. As such, the Committee did not agree with the subject company's interpretation that the Code Committee's findings were inconsistent with the Guidance.
- The Appeals Committee also noted the subject company's view that its offer of corrective action during the ICD process was likely to have resolved this aspect of the complaint. The Committee noted that the subject company had not appealed the Code Committee's findings on the ICD process and that accordingly its remit, as defined in Section 15.7, did not extend to the ICD process.
- Notwithstanding the above, the Committee considered the subject company's submission that the matters it suggested in ICD to resolve the complaint would have done so. Those included correcting references to 'meta-analyses' to 'network meta-analyses', removing Burnett and redrafting the headline claim. The Committee noted that while each of those proposed amendments would go some way to resolving the issues complained of, it was not for the Committee to determine what claims could or could not be made in promotional material (that is, to engage in redrafting), or to speculate on whether amended promotional materials would or would not contravene the Code. That is a matter for companies. In any event, the materials had already been published, and it was appropriate for the Committee to consider the complaint.

Use of ORION-3

- Each advertisement featured insights from the ORION-3 trial, including a prominent side-by-side graphic comparing LDL-C reduction rates:

  (i) "61%... with Repatha... Year 1";
  (ii) "45%... with inclisiran... Years 2-4"; and,
  (iii) "44 %... with inclisiran... Years 1-4".

- The 61% figure was displayed in bright red colour, while the 45% and 44% figures appeared in grey.

Use of ORION-3 (continued)

- The Appeals Committee affirmed the decision made by the Code Committee, being that the ORION-3 data was not presented fairly or accurately. The Committee noted that the subject company maintained its belief that ORION-3 represents an appropriate level of evidence to support the comparative claim made in the materials. The Committee disagreed. The comparisons in the graphic spanned different time points, treatment stages, patient populations and prior treatment exposures, such that the patient groups in the cited studies were inappropriate for side-by-side comparison in the manner presented. The result was misleading and failed to support proper assessment of the product's risks and benefits. **The Appeals Committee unanimously determined that this constituted a breach of Overarching Principles 3 and 7.**
- The Committee further found that the Code Committee's reasoning does not prevent the subject company from using ORION-3 to support promotional claims for Repatha. While recognising the practical challenges of referencing material associated with a determined breach, the Committee affirmed that the finding related to the strong comparative presentation of outcomes derived from data not designed or powered for that purpose, rather than to the validity or relevance of ORION-3 itself.
- The Committee acknowledged the sentiment expressed by a healthcare professional (in a letter relied upon by the subject company on appeal) that "*ORION-3 provides clinicians with valuable and important information relevant to clinical practice … and … evidence to support clinical decisions and counsel patients about switching from Evolocumab to Inclisiran.*" The Committee further noted that there appeared to be general agreement among the parties that the usefulness and value of the ORION-3 data were not in question.
- However, because visual presentation is such a powerful communication tool, it is important that visual elements are used accurately, responsibly, and in a scientifically valid context - standards that the Committee considered were not met in this instance. The data referred to were not designed or powered for the outcomes to be presented in the way that they were, which gave the impression of a direct efficacy comparison.
- The Committee acknowledged that the materials noted limitations of the data, including that ORION-3 was not a head-to-head trial, but they also noted it failed to include a key limitation highlighted in the ORION-3 paper: "*This study also did not formally provide a randomised comparison between evolocumab and inclisiran but instead used switching to assess ease, safety, and efficacy of treatment transition in a single arm. Formal comparisons of efficacy would require a dedicated 3-arm trial with two active comparator arms and placebo. Finally, it is worth noting that patients in the inclisiran-only arm of ORION-3 received their last injection of inclisiran in ORION-1 at least 9 months to 1 year earlier and did not receive the normal day 90 dose that is used de-novo to initiate inclisiran. Instead, patients went straight to a 6-monthly maintenance dosing regimen.*"
- Overall, in keeping with the Code Committee's decision, the Committee determined that inclusion of these statements did not counteract or justify presenting a direct comparison of the efficacy of Repatha and inclisiran in the strong visual graphic used, which overstated the strength of the evidence.
- With regard to the subject company's assertion about "*the Committee's conclusion that the data were conflated*," the Appeals Committee clarified that its concern related specifically to the infographic displaying three side-by-side statistics derived from data that should not have been presented together in that manner, as it created an impression of Repatha's superiority over inclisiran. The Committee did not interpret this concern as relating to the tables or results presented elsewhere (in the materials) in graphical form.

Use of ORION-3 (continued)

- The Committee affirmed the Code Committee's determination that the ORION-3 data was not presented fairly or accurately. ORION-3 was a long-term extension of the ORION-1, which included eight treatment arms with varying doses and small patient numbers. Accurate interpretation of ORION-3 requires consideration of the methodology of ORION-1, meaning any observed differences through ORION-3 should be interpreted as exploratory rather than confirmatory. Additionally, comparisons were made across different time points, treatment stages, and prior treatment exposures, which were not appropriate for side-by-side presentation as they were in the materials (e.g., year 1 vs. years 2–4). This approach resulted in a misleading representation that did not support a proper assessment of the product's risks and benefits.
- The Appeals Committee also noted that comparative promotional material is permitted under the Code. Any comparative statements need to be presented in a fair and just manner, and extra care must be taken to ensure that any comparison properly reflects the body of evidence and does not mislead by distortion, by undue emphasis or in any other way. Whilst the Code does not specify that certain types or levels of substantiating data are required to support different types of claims, the Medicines Australia Guidance does emphasize that "*a comparative claim that one product is more effective or better tolerated than another should be substantiated by unequivocal evidence regarding the claimed superiority of the product.*"

Sanctions

- The subject company submitted that the sanction imposed by the Code Committee ought to be varied such that any breach arising from the materials be considered a minor breach and the monetary fine should be reduced.
- The Appeals Committee, having unanimously affirmed the decisions made by the Code Committee, nonetheless reviewed the classification of those breaches. The Code defines breaches as minor, moderate, or severe. The Committee determined that as the breaches "may have a moderate effect on how the medical profession will prescribe the product," they were appropriately categorised as moderate. It was considered unreasonable to conclude that the breaches would have "no or minimal effect on how the medical profession will prescribe the product," which is the criterion for a minor breach.
- With regard to the quantum of the fine, the fact that steps were taken by the subject company 'in good faith during the ICD process' was taken into account by the Code Committee in determining the fine, noting the fine imposed was not the maximum fine available to them.
- In addition, although the Code Committee did not require corrective action, this fact doesn't necessarily diminish the level of fine. Sanctions are applied as a package to ensure the overall outcome is proportionate. For example, where corrective action such as issuing a corrective letter is required, the Committee may determine that a lower fine is appropriate to balance the total sanction, and vice versa.
- The Committee therefore affirmed the Code Committee's decision and the sanctions imposed.

    (i) Single monetary fine of $130,000.
    (ii) Withdrawal of the materials found in breach (where they are still in circulation) as well as any other promotional material containing the claims found in breach
    (iii) The content found in breach must not be used in the same or similar form.

- With regards to the Appeal bond of $20,000 paid by complainant, the Appeals Committee instructed this appeal bond be retained by Medicines Australia, reflecting the outcome of the appeal.

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