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COMPLAINT OUTCOME

1173 - Promotional material related to ERYLAND

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 20 November 2023 and an extract of the minutes of the appeal heard by the Appeals Committee on 9 February 2024.

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The Code of Conduct and all associated materials are available on the Medicines Australia website

COMPLAINT 1173 Promotional material related to ERYLAND

SUBJECT COMPANY	PRODUCT	COMPLAINANT
Janssen	ERLYAND (apalutamide)	Bayer

COMPLAINT

Bayer was concerned by Janssen's use of a claim related to their product Erlyand, which was used in a 1- page advertisement or banner/conference panel with a single claim and qualifier.

Bayer argued that using the claim in isolation was inappropriate, as it was derived from an exploratory sensitivity analysis that was conducted outside of the statistical hierarchy for the study and hence is uncontrolled for type 1 error. Bayer believed that any use of the claim should be in the context of the coprimary OS endpoint, and with a transparent qualifier noting its evidentiary limitations (exploratory sensitivity analysis reported with a nominal p-value). Bayer alleged that the use of the claim in isolation breaches the Code, arguing that it potentially could have a significant impact on prescribing and therefore that these alleged breaches were severe.

SECTIONS OF THE CODE (EDITION 19)

- **Overarching Principle 2**: Companies are committed to transparency in their interactions with healthcare professionals and other stakeholders, to maintain trust and confidence in the industry.
- **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**: Requirements for Promotional Claims Directed at Healthcare Professionals
- **Section 1.1**: Substantiating Data
- **Section 2**: Requirements For Material Directed To Healthcare Professionals

RESPONSE TO THE COMPLAINT

Janssen disagreed that the analysis was exploratory. Janssen was of the view that it was a pre-specified analysis and clearly stated in the study's analysis plan. In addition, "the claim also clearly states the relative reduction in the risk of death is after cross over based on an IPCW analysis in the qualifier leaving no doubt in the reader's mind upon which it is based". Janssen asserted that the co-primary endpoint was met, the claim clearly articulated the data and its setting, and was appropriately qualified and referenced. The claim therefore did not mislead the audience or misrepresent the information. In addition, a summary of the study findings is provided in wording within the Erlyand Product Information.

Janssen expressed concern over procedural issues, because new issues were raised in this complaint that had not been raised in intercompany dialogue (ICD), where Bayer digressed from the formal procedure for ICD, and Bayer's concerns continued to evolve.

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 3-5.

APPEAL

The subject company appealed all the findings of the Code Committee. The complainant did not appeal any findings of the Code Committee but in their appeal response they highlighted two inconsistencies with the Code Committee's Reasons:

(i) The claim omits the primary endpoint entirely, rather than de-emphasizing it, and

(ii) The Code Committee's use of the descriptor "exploratory" is inconsistent with the wording in the required sanctions.

APPEAL COMMITTEE DECISIONS

The Appeals Committee upheld all findings of the Code Committee, reconfirming breaches of the Code. The sanctions were upheld, albeit with clarified wording (see page 8). The Reasons for their Decisions are on pages 5-8.

Code	Code Committee Decision	Code Committee Sanctions	Appeals Committee Decision	Appeals Committee Sanctions
Principle 2	Breach Unanimous	• $150, 000 fine (moderate breach) • Janssen to cease using the claim in isolation from the coprimary endpoint OS result • Janssen to cease using the claim without a prominent qualifier clarifying that this is an exploratory sensitivity analysis reported with a nominal p-value	Breach Unanimous	• $150, 000 fine (moderate breach) • Janssen to cease using the claim: a) in isolation from the coprimary endpoint OS result, and b) without a prominent qualifier clarifying that this is an exploratory sensitivity analysis.
Principle 3	Breach Unanimous		Breach Unanimous	
Principle 7	Breach Majority		Breach Unanimous	
Section 1	Breach Unanimous		Breach Unanimous	
Section 1.1	Breach Unanimous		Breach Unanimous	
Section 2	Breach Unanimous		Breach Unanimous	

With regards to the Appeal bond of $20,000 paid by the subject company, the Appeals Committee instructed that this be retained by Medicines Australia, because the Code Committee's findings were upheld.

CONSIDERATION OF THE COMPLAINT by the CODE COMMITTEE

- The complaint concerned the use of a claim ('the Claim') related to Janssen's product Erlyand in promotional materials including a 1-page advertisement and banner/conference panel.
- The Claim is: "*Erlyand (apalutamide) reduces the relative risk of death by 48% in a broad mHSPC patient population (OS after cross over correction HR=0.52; p<0.0001, in combination with ADT)*" ('the Claim'). The complainant alleged that the use of the Claim in isolation was not appropriate because it was derived from an exploratory sensitivity analysis conducted outside the statistical hierarchy for the study and was uncontrolled by type 1 error.
- The complainant alleged four detailed concerns with the Claim. However, the complainant was not able to demonstrate that all four concerns were raised with the subject company through intercompany dialogue ('ICD'). Because of this, Medicines Australia directed the Code Committee to only consider the two concerns featured in ICD, to which the subject company had the opportunity to respond. Those concerns were:

    (a) The reported reduction in risk of mortality is markedly greater in the Claim than that reported for the co-primary endpoint for which the study was powered and designed.
    (b) The analysis on which the Claim is based was an 'exploratory sensitivity analysis' and the published statistical analysis plan states that efficacy analyses will be performed in the ITT population, which is the case for the co-primary result but not the data cited in the Claim.

- The subject company raised procedural concerns with the way the complainant approached the complaint, namely the addition of new concerns after ICD had concluded (see previous point), a preference to digress from procedure for face-to-face ICD, and an evolving approach to applying different principles and sections of the Code to the complaint. The subject company did not, however, make a specific allegation that the complainant had breached the Code. The Committee therefore noted that there was no matter before it to decide in relation to these concerns, including because the Committee had been directed by Medicines Australia not to consider the new concerns. Regardless, the Committee reiterated that all companies should follow ICD guidelines and undertake fair and respectful discussions that make a genuine attempt to resolve the dispute, before complaining to Medicines Australia and seeking adjudication by the Committee.

Concern 1 – reduction in risk of mortality, as presented.

- The Committee noted that the results obtained in the study were significant and impressive. However, the Committee identified that the reported reduction in risk of mortality ('RRR' 48%) referred to in the Claim was markedly greater than that reported for the co-primary endpoint (RRR 35%).
- The Committee determined the material emphasised the prespecified sensitivity analysis results and minimised the primary outcome, and did so through the presentation of that data, which had the effect of de-valuing the primary outcome. For example, the pre-specified sensitivity analysis is embodied in the Claim and features in bold font, whilst the primary outcome is in a lighter shade of font, presented in brackets and only after the pre-specified sensitivity analysis is featured prominently. The Committee also noted this presentation was not in accordance with the way the sensitivity and primary outcomes were presented in the Product Information ('PI').
- The Committee noted that whilst the complainant referred to this as "*an exploratory sensitivity analysis*", the most appropriate term is "*pre-specified sensitivity analysis*" which is consistent with the publication for the TITAN study in the paper reporting 'Final Survival Analysis ….of the TITAN Study.
- Accordingly, the Committee considered that the Claim as used was not appropriate because the actual primary outcome as measured by the ITT analysis was presented in a way that was significantly de-emphasised, so that a reasonable audience would not be able to interpret the data based on a pre-specified sensitivity analysis when the primary outcome ITT analysis was devalued as noted.
- The Committee also considered the study design and study plan in order to evaluate whether the analysis on which the Claim was based could be used in the way it was. Whilst it was noted that the study did pre-specify the analyses as part of the statistical analysis plan for the trial, and this was planned for and written in that plan prior to the unblinding of the study, the Committee took the view that pre-planned or otherwise, generating a major claim on sensitivity analysis was not adequately substantiated.
- In relation to the allegation that the data "*cited in the Claim was not in the Erlyand approved Product Information*", the Committee agreed that the actual statistical data for the prespecified sensitivity analysis were not presented in the PI. The statistical analysis for the Primary outcome (Intention To Treat analysis) was presented.

Concern 2 – use of pre-specified sensitivity analysis

- The Committee considered that the specified sensitivity analysis and not the primary outcome had been given greater emphasis in the Claim because the percentage reduction in mortality was greater. In doing so, the Committee considered that the data referred to in the Claim were overstated.
- The Committee also determined that the use of the Claim was not substantiated sufficiently to be used as a major claim without presenting adequately the overall context of the coprimary Overall Survival ('OS') endpoint, for which the study was powered and designed.
- The Committee acknowledged that presenting the primary outcome analysis remains an integral element of a study and there is a general expectation that it should be provided to give healthcare professionals the context they need to understand any other data accordingly. Whilst the RRR derived from the sensitivity analysis used in the Claim corrects for the bias created due to a large proportion of patients' crossover and is considered reliable and significant, the Committee did not accept that this justified the overemphasis in the Claim when compared with the primary outcome analysis.
- The Committee further determined the Claim lacked sufficient emphasis to enable a healthcare professional to understand that it was derived from sensitivity analysis data, and therefore obscured the significance of the primary outcome data.
- Furthermore, as the coprimary data was de-emphasised, the Committee did not believe the qualifier and the footnotes together provided a complete picture for healthcare professionals to fully understand the meaning and relevance of the Claim. The Committee confirmed that the onus is on the company to provide sufficient detail to enable a reader to understand the significance of the data.
- The Committee considered that its' findings were not intended to prevent the use of the Claim in the future, however, any future use of the Claim must be fairly presented in the context of the coprimary OS endpoint, and with a transparent qualifier noting its evidentiary limitations (pre-specified sensitivity analysis)

Relevant principles and provisions of the Code

- In light of the findings set out above, the Committee determined that the use of the Claim in promotional material comprised a breach of the following principles and provisions of the Code:

(a) **Principle 2**: the Committee considered that the Claim was not transparent and therefore a breach of Principle 2 had occurred, namely that there was a lack of transparency in interactions with healthcare professionals, relevant to maintaining trust and confidence in the industry.

(b) **Principle 3**: while the Committee considered that the data presented were valid, it determined that the material was not balanced, for the reasons set out above.

(c) **Principle 7**: the Committee considered that the Claim did not enable proper assessment of the benefits of the product, for the reasons set out above.

(d) **Section 1**: the Committee considered that the Claim was not balanced and misled by omission, and that the numerical data cited in the Claim are not cited in the Product Information.

(e) **Section 1.1**: the Committee referred to three reasons posed by the complainant as to why this section had been breached namely:

(i) Comparative claims based on studies reporting clinically important differences must include sufficient detail to enable the reader to understand the significance of the data;

(ii) Claims based on statistical comparison must include sufficient detail to ensure the reader to understand the statistical significance of the data; and

(iii) The accepted level of statistical significance is $p < 0.05$ and for multiple comparisons will be lower.

The Committee considered that for reasons (i) and (ii) there was a breach of this section. The Committee did not consider (iii) due to Medicines Australia's direction regarding procedural concerns; and

(f) **Section 2**: the Committee determined that, for the reasons set out above, the Claim was not presented in such a way that visible information is accurate and consistent with the Code when read in isolation.

Sanctions

- The Committee considered that the primary impact of the use of the Claim would be commercial, that is, encouraging the prescribing of the product, rather than having an effect on patient welfare as such. Nonetheless, in circumstances where the Committee was satisfied the Claim may affect how the medical profession prescribes the product, the breach was categorised as moderate.
- The Committee considered whether a sanction was appropriate, having regard to the following factors:

  (a) Whether the breach should have been clearly evident to the subject company;
  (b) Length of time that the materials have been in use;
  (c) The number and type of alleged breach/es;
  (d) Circumstances in which the Claim was used – and the explanation offered by the subject company; and
  (e) Where prescribing behaviour is affected, the likely degree of the effect.

- The Committee determined that a fine was appropriate, at the high end of the moderate category threshold (as imposed by the Code). The Committee imposed the following sanctions:

  (a) a single monetary fine encompassing all breaches, in the amount of $150,000;
  (b) a requirement for the subject company to:

    (i) cease use of the Claim in isolation from the coprimary endpoint OS result; and
    (ii) cease use of the Claim without a prominent qualifier clarifying that this is an exploratory sensitivity analysis reported with a nominal p-value.

CONSIDERATION OF THE COMPLAINT by the APPEALS COMMITTEE

The appeal material and appeal process

- Section 16.6 provides that an appeal is a rehearing of the original complaint, and 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 noted previous Appeals Committee decisions have been communicated as a Committee decision. On this occasion, the Committee determined it appropriate to communicate the unanimous nature of all decisions made at the meeting. The Committee achieved consensus on all decisions considered in this appeal.

The findings in relation to the Claim

- The Appeals Committee noted the importance of Overall Survival (OS) percentage in the oncology landscape, and subsequently the importance of ensuring that any percentage being provided to healthcare professionals is accurate, balanced, and scientifically valid.
- The core of the complaint is that the Claim is communicated without the required context.
- The Appeals Committee unanimously agreed that the required context for this Claim was to provide the co-primary endpoint Overall Survival result and use a prominent qualifier to clarify that the Claim is derived from an exploratory sensitivity analysis. The Committee accepted that this was a standard expectation of the scientific community, and without this context, a clinician is unlikely to fully understand the context of that claim.
- The Appeals Committee noted that this approach was in part understood by the subject company, as documented in their complaint response: "*However, in the interest of transparency and following standard practice, the ITT result is still faithfully reported, but the limitations underlying this result should always be acknowledged.*"
- The Appeals Committee reaffirmed the decisions made by the Code Committee in their entirety.

Concern 1 – the Code Committee has misinterpreted the Claim

- The subject company alleged that the Code Committee incorrectly interpreted the text in brackets (circled in red in Figure 1) as the primary outcome '*...in a lighter shade of font, presented in brackets and only after the pre-specified sensitivity analysis is featured prominently*'.
- Both the subject company and the complainant agreed that the entirety of the Claim, including the text in brackets, is derived from the pre-specified sensitivity analysis, and does not include a reference to the co-primary endpoint.
- The Appeals Committee agreed that the Code Committee had erred in its interpretation of the Claim, mistaking the qualifier statement to be a reference to the primary outcome.

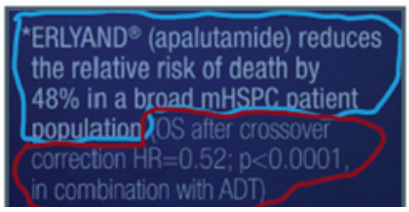

Figure 1: The Claim as presented in the promotional material

- However, this misinterpretation did not affect the view of the Code Committee that the primary outcome was de-emphasized and should be made clear. The Appeals Committee agreed that the absence of the study's primary outcome in the Claim was more egregious than a scenario where it was de-emphasized and did not have implications on the rationale for the remaining findings.

Concern 2 – Inconsistencies in the ruling and principles of the Code relating to Janssen's use of a pre-specified sensitivity analysis of the co-primary endpoint as a promotional claim

- The subject company alleged that one of the sanctions directed by the Code Committee, to cease using the Claim in isolation from the co-primary endpoint Overall Survival result, was inconsistent with Code Edition 19. Specifically, it argued the wording and intent within the Code in Section 1.1 is in contradiction with the Code Committee's requirement to add the co-primary endpoint Overall Survival result to the Claim.
- The Appeals Committee noted that Code Edition 19 Section 1.1 does discuss claims based on pre-specified secondary endpoints, but also noted these principles were not relevant to the Claim because the primary endpoint ***was*** met, and the Claim is based on a pre-specified ***sensitivity analysis*** of a primary endpoint rather than a pre-specified secondary endpoint.
- The Appeals Committee considered the excerpt provided by the subject company which they used to demonstrate the intent of Code Edition 19, being Section 1.2.2 of the Code Edition 18 Guidelines, titled 'Secondary Endpoints and post-hoc analyses'. Particularly "*...if the primary endpoint was met, the qualification may not be required...*"
- Noting this, the Appeals Committee determined the phrase '*may not be required*' was not as critical as the phrase: "*However, further qualification may still be required to ensure a reader fully understands the context of the claim*". In the context of the Claim, the Committee determined that there was insufficient context provided to ensure a healthcare professional understood the Claim.
- The guidance utilised by the subject company in Code Edition 18 Guidelines was applicable to 'Secondary Endpoints and post-hoc analyses'. The Appeals Committee noted the Claim was neither post-hoc, nor utilising a secondary endpoint. It was not appropriate to conflate secondary endpoints with that for sensitivity analyses of endpoints.
- Furthermore, the Appeals Committee rejected the notion that Code Edition 18 Guidelines specifically referred to crossover scenarios in the below text (Figure 2). The Appeals Committee clarified that the clause relates to a trial that has stopped prematurely due to a pre-defined threshold being achieved for a non-primary outcome, and not a trial that by study design has incorporated a cohort of patients crossing over from one study arm to another. They also noted this clause relates to a controlled trial stopping early and this was not the precise case for the TITAN Study, where unblinding was performed after the first interim analysis based on a primary outcome, overall survival, reaching early statistical significance.

It may be acceptable that in the case of an appropriately designed and conducted randomised controlled trial stopped early due to benefit on a non-primary outcome crossing a pre-defined threshold; this result may be communicated without reference to the primary endpoint. However further qualification may still be required to ensure a reader fully understands the context of the claim.

Figure 2: Edition 18 Guidelines, Section 1.2.2

- Whilst the Committee understood companies referring to previous editions of the Code and its Guidelines to support clearer direction, in this instance, it was not an appropriate application upon which to depend. In conclusion, the Appeals Committee determined that the subject company had incorrectly applied the wording and intent of the Code Edition 18. They also noted Edition 18 and its Guidelines were superseded by Edition 19 and therefore is non-binding advice.
- Because of this, the Appeals Committee did not share the view put forward by the subject company, that "*the Code Committee's decision will set a precedent for all companies to clearly specify the results of the primary endpoint if making a claim based on pre-specified analyses, regardless of the primary endpoint outcome*". Instead, the Appeals Committee determined the nature of an individual study's design and analyses was key to determining the sufficiency of contextual qualification of any promotional claim.
- The Appeals Committee determined that the Claim lacked sufficient context (such as primary endpoint analysis and evidentiary limitations), to be accurately interpreted by its intended audience, and in its current form misled by omission.

Concern 3 - The Code Committee did not consider the statistical and clinical context of the Claim

- The subject company put forward its belief that the statistical and clinical context of the Claim led to "*a more realistic view of the treatment effect between (study) arms that clinicians should use in their decision-making process*" and alleged that the Code Committee did not consider the statistical and clinical context of the Claim.
- In response, the Appeals Committee confirmed their understanding that the TITAN study allowed patients to 'cross-over' from the control arm to the apalutamide arm after the first interim analysis. The Appeals Committee noted a statistical method of *Inverse Probability Consensus Weighting (IPCW)* was used to estimate the influence of treatment arm crossover on overall survival, which resulted in the efficacy estimate that formed the basis for the Claim.
- The Appeals Committee supported the view of the Code Committee that this methodology, and other similar statistical methods, have value in understanding the true effect of the overall survival benefit. However, the Appeals Committee noted these analyses are complex as they employ processes to construct a quasi-control arm that models what the treatment effect might have been had treatment crossover not occurred. This requires reliance on assumptions that are practically challenging to justify in the context of a large clinical trial. While these methods generally have less bias than naïve statistical approaches to adjust for crossover, they are not accepted without limitation across the clinical and scientific community.
- Therefore, while it may be '*significant and appropriate*' to '*communicate a more realistic view of the survival benefit to guide clinicians in their decision-making process, which is to generate a claim based on the pre-specified sensitivity analysis*', the Claim should not be made in isolation from the primary outcome analysis, and it should be made clear that any such data is derived from an exploratory analysis.
- Since the Claim was made in isolation from the primary outcome analysis, the Appeals Committee reconfirmed the view that the Claim was overstated. The Committee noted that had the Claim been communicated alongside the co-primary endpoint Overall Survival result and qualified by stating it is based on an exploratory sensitivity analysis, this conclusion may not necessarily have been drawn.
- The Appeals Committee clarified its interpretation that generating a major claim based on sensitivity analysis without presenting adequate context is the primary reason for determining that there was insufficient substantiation, not the data itself. The data from which the Claim was generated does sufficiently substantiate the Claim, but only if presented with the overall context of the co-primary Overall Survival endpoint, for which the study was endorsed and designed.
- The Appeals Committee confirmed the Code requires that promotional claims are '*consistent with the Australian Product Information document*'. Whilst the actual statistical data for the prespecified sensitivity analysis was not presented in the Product Information, it may still be consistent with the Product Information. As this was not part of the appeal, the Committee did not consider this in detail, insofar as to clarify that the statistical analysis for the Primary outcome (Intention To Treat analysis) was presented in the Product Information, and the prespecified sensitivity analysis was not, confirming the importance and prominence of communicating the Primary Outcome alongside an exploratory analysis.

Concern 4 – The level of fine was excessive, and sanctions contained error

- The subject company argued that the fine of $150,000 was excessive and requested the Appeals Committee reconsider the sanctions. They also noted that sanction included the requirement to report a nominal p-value, which should not have been considered by the Code Committee and was, therefore, an error. The term used in the sanction "*exploratory sensitivity analysis*" was in contradiction to the Code Committee's clarification it considered the study to be termed a "*pre-specified sensitivity analysis*".
- The Appeals Committee determined the analysis was pre-specified (the sensitivity analysis was pre-determined before the study results, and was not post-hoc), was exploratory (the data was not observed or measured but used statistical methodology to adjust for the crossover), and was a sensitivity analysis (this was not in question).
- The Appeals Committee appreciated that a combination of different terms has been used, and each party to the complaint had different preferences. In response to this difference in terms, the Code Committee deemed that the most appropriate term is "pre-specified sensitivity analysis", but ultimately all three descriptors are correct (exploratory, pre-specified and sensitivity), and all had been used in different formats, publications, and correspondence.
- Therefore, the Appeals Committee determined that the Code Committee's sanction requiring the subject company to cease using the Claim "*without a prominent qualifier clarifying that this is an* ***exploratory sensitivity analysis***" was not incorrect. This requirement represents the minimum way to describe the analysis and even if the subject company added "pre-specified" to this qualifier, the Code Committee's sanctions would remain appropriate.
- The Appeals Committee considered the inclusion of '*nominal p-value*' in the sanctions issued by the Code Committee, and determined this inclusion should be removed due to it being excluded from the inter-company dialogue between the parties, and therefore the Code Committee discussions.
- The Appeals Committee agreed with the Code Committee's categorisation of a moderate breach, because the Claim may affect how the medical profession prescribes the product.
- The Appeals Committee also agreed that the five factors, as listed in the Code Committee's Reasons were relevant and appropriate to determine the fine amount.
- The Appeals Committee agreed unanimously that a fine at the high end of the moderate category threshold (as outlined in the Code) was appropriate and endorsed the rate of $150,000 as determined by the Code Committee.

- end -