COMPLAINT OUTCOME

1168 - TRELEGY ELLIPTA 200 Promotional Materials and Abuse of the Code

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 the Subject Company has advised Medicines Australia that they will not appeal the outcome of the Code of Conduct Committee decision (following circulation of the Code minutes) or, in the case of an appeal, the minutes of the Appeals Committee meeting have been provided to both parties.

This report is an extract of the minutes of the complaint heard on 16 January 2023.

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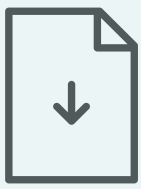

DOWNLOAD THE CODE

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

COMPLAINT 1168 TRELEGY ELLIPTA 200 PROMOTIONAL MATERIAL and ABUSE OF THE CODE

SUBJECT COMPANY	PRODUCT	COMPLAINANT
GSK Australia (GSK)	TRELEGY ELLIPTA (fluticasone furoate, umeclidinium, and vilanterol inhalation powder)	Chiesi Australia (Chiesi)

COMPLAINT HAS 2 PARTS

(i) Chiesi alleged that promotional materials for TRELEGY ELLIPTA are in breach of principles 1 and 3, and sections 1 and 1.11 of the Code because (in summary) they are 'misleading, unbalanced and do not support the quality use of medicines'. The complaint related to 3 types of promotional materials; a clinical study folder, a promotional leave-behind and a video.

With respect to the clinical study and leave-behind, and in summary, Chiesi alleged that three major claims are based on post-hoc analysis without clear statistical significance and referenced solely to a poster which is not identified as unpublished post-hoc analysis. Chiesi submitted that the claims should be appropriately substantiated. Chiesi also submitted that the claims as made in the promotional material were more favourable than the results of the pre-specified endpoints published in the study relied upon, and therefore that claims were selectively highlighted to misrepresent the clinical benefit of the product. Further, Chiesi submitted that the promotional material did not make sufficiently clear that the comparison of the highest dose triple therapy is compared with the lowest dose dual therapy, and that this was misleading. The use of a 7-day study was said to be "*not clinically meaningful on its own to support the claims of superiority…*"

With respect to the promotional video, Chiesi submitted that the study featured in the video was not designed to assess efficacy and safety between molecules and again, that the use of the 7-day study was misleading as noted above.

(ii) Chiesi also alleged that GSK has abused and mis-used the Medicines Australia complaints process by pursuing a series of frivolous and vexatious promotional challenges against Chiesi "*that are intended to disrupt Chiesi's business … with the timings of these complaints exclusively corresponding to key Chiesi events either immediately prior to or at commencement of local product launches and/or coincided with Australian public holidays*", said to be in contravention of section 16.4 of the Code.

With regards to acceptance of complaints, Chiesi alleged that GSK had breached the Code by putting forward a complaint to Medicines Australia (Jan 22) which had, in part, already been resolved through intercompany dialogue, said to be in contravention of section 16.1 of the Code.

SECTIONS OF THE CODE

EDITION 19

- **Overarching Principle 1** : All activities undertaken by Companies have the purpose of supporting the quality use of medicines.
- **Overarching Principle 3**: Companies are responsible providing current, accurate, balanced, and scientifically valid information products to support their use.
- **Section 1**: Requirements for promotional claims directed at healthcare professionals
- **Section 1.1**: Substantiating data
- **Section 16.1**: Acceptance of Complaints
- **Section 16.4**: Abuse of the Code

RESPONSE TO THE COMPLAINT

(i) GSK maintained that promotion using pre-specified comparison groups of the primary, key secondary and other secondary endpoint data is scientifically robust and balanced, clinically relevant, contained within the Trelegy ® product information and aligned with the Code, as well as local asthma guidelines. It maintained that the data provided statistical rigour, was not post-hoc in nature, and that claims were substantiated from more than 1 reference.

GSK also submitted that parts of the complaint raised by Chiesi had been addressed in intercompany dialogue and that its complaint involved "*re-opening of resolved matters have occurred and consensus positions misrepresented*". In particular, GSK submitted that the video was "*a resolved matter and should not be put forward for adjudication by the Code Committee as per MA complaints guidance*".

(ii) GSK refuted any suggestion of 'abuse of the Code'. It referred to 4 rounds of intercompany dialogue to address complaints that had been raised by GSK, with respect to "ongoing and related breaches of previous complaints that had been resolved and subsequently found again in field". In addition, GSK argued that the Committee would not be able to make a finding on frivolous and vexatiousness activity pursuant to section 16.4 of the Code, without having first found a series of complaints unwarranted and baseless. GSK noted that Chiesi had elected not to have GSK's complaints (which provided the basis for this limb of Chiesi's complaint) heard by the Committee, in circumstances where Chiesi was not a member company.

CODE OF CONDUCT COMMITTEE DECISIONS

Complaint	Committee Decision
1. Distribution of promotional materials that are misleading, unbalanced and do not support the quality use of medicines.	
(a) Three major claims are based on a post-hoc analysis referenced solely to a poster which are not clearly identified as an unpublished post-hoc analysis, details of the analysis are not provided, and statistical significance of the results not clear. Misleading through the comparison of the highest dose triple therapy being compared to the lowest dose dual therapy. **CAPTAIN Clinical Study Folder and Leave Behind*	Unanimous decision Overarching Principle 1: Breach Overarching Principle 3: Breach Section 1: Breach Section 1.1: Breach
(b) Study by Daley-Yates et al, 2021, is not clinically meaningful in relation to supporting the claims of clinical superiority. Comments in the video are unbalanced and misleading. **Video*	The Committee determined to consider the complaint regarding the video insofar as that complaint sought that GSK '*refrain from using the pharmacology study to support claims of clinical superiority*'. Unanimous decision Section 1: No breach Section 1.1: No breach
2. Abuse of the Code and misuse of the complaints process by pursuing a series of frivolous and vexatious promotional challenges.	
(a) Acceptance of the complaint; GSK submitting a complaint including items already resolved.	Unanimous decision Section 16.1: No breach
(b) Abuse of the Code; Consistently raising issues that are iintended to disrupt Chiesi's business – timing them maliciously.	Unanimous decision Section 16.4: No breach

SANCTION	The Committee unanimously agreed that the breaches were classified as moderate, having regard to the potential impact this would have on the way a healthcare professional may prescribe the product. The Committee considered the merits and limitations of a corrective letter, and made a majority decision not to impose the sanction of a corrective letter. The Committee agreed unanimously to impose the following sanctions: • Cease using all materials found in breach (where they are still in circulation) and not use the claims in the same or similar format in future materials. • Pay a fine of $150,000 (exc GST)

CONSIDERATION OF THE COMPLAINT

Complaint 1(a): Three major claims are based on a post-hoc analysis referenced solely to a poster which are not clearly identified as an unpublished post-hoc analysis, details of the analysis are not provided, and statistical significance of the results not clear. Misleading through the comparison of the highest dose triple therapy being compared to the lowest dose dual therapy.

The Committee noted that intercompany dialogue has occurred regarding the Clinical Study Folder and the Leave Behind and understands that whilst GSK has agreed to modify some technical aspects to better align with the MA Code (including additions to improve clarity of statistical analysis), GSK remained of the view that the material is compliant with the MA Code, with regards to balance and appropriateness of information contained within the promotional pieces.

The Committee noted this part of the complaint refers to three prominent claims in the Clinical Study Folder and the Leave Behind being large clinical improvements in lung function (143 mL), asthma control (64%) and exacerbations (37%) compared to a dual therapy inhaler. The claims were prominent headline claims in both sets of promotional material, which should therefore be substantiated to an equivalent level of substantiated evidence.

The CAPTAIN Study was discussed and the Committee understands this to include 4 different data comparisons. While the promotional pieces referenced the Study, they also included additional comparative analysis not presented in the original peer-reviewed published study, but presented in a later poster presentation. In doing so, the promotional pieces made claims that relied on a comparison of different dosing regimes to support a headline efficacy figure. The Committee noted that to be consistent with the Quality Use of Medicines, comparisons that use doses should incorporate comparison of equivalent dosage, rather than a comparison of lower doses (within the dual therapy) to higher doses (within the triple therapy), to allow clinically meaningful, balanced and fair comparative results. The Committee noted that while the data presented in the materials was strictly accurate, the dosing comparison did not lead to a scientifically or clinically appropriate comparison. The comparison was presented in a prominent way, and the Committee members were of the view that this was misleading, and of concern in circumstances where a busy healthcare professional may not identify that different dosing regimens were referenced.

The Committee discussed that a healthcare professional should expect a Clinical Study Folder to clearly identify the study's primary and secondary outcomes, and then clearly state any exploratory post-hoc outcomes. In this regard, the Study Folder appeared to conflate non-primary outcomes which potentially creates confusion. The Committee was of the view that the material should make clear the CAPTAIN study primary outcomes, including the clinically relevant dose comparisons. For presented secondary or exploratory outcomes, such as exacerbations, material should present in a manner clear to a receiving healthcare professional where primary outcome statistical testing was not met (and p-values are hence nominal).

In addition, all three claims are significantly more favourable than the resultsclinically appropriate comparative-dose endpoints, it was not appropriate to generate prominent claims from a Study's exploratory data rather than primary or secondary endpoints. This was compounded by the statistical insignificance of higher hierarchical outcomes not being clearly communicated. Some members expressed further concern about the way the exacerbation data was expressed as the CAPTAIN study highlighted the ICS dose to be highly correlated to exacerbation rate and the presentation of the material would mislead a clinician to overestimate the benefit of triple therapy.

CONSIDERATION OF THE COMPLAINT continued ...

The Committee was also concerned that a conference poster had been used as a substantiating reference. Whilst the data referred to was found in the Study, the results of the statistical analysis including the p-value, which is the highlighted finding, were derived only from the poster.

The Committee again discussed the likelihood that the materials may lead a busy healthcare professional to form the impression that Trelegy Ellipta 200 provides medical superiority based on the choice of comparisons and the prominent headline claims derived from that data, and therefore may influence prescribing behaviour. Views were further expressed that the font size and organisation of the information made it difficult to discern the basis for the statements made, and the data presented was essentially "cherry-picked" from the multiple secondary analyses to highlight the results in a more favourable manner than could be reasonably be inferred from the primary analysis. However the Committee was not of the view that patient safety was compromised.

The Committee reached a unanimous decision that the Folder and Leave Behind were poorly presented, and on balance, were misleading and in contravention of Sections 1 and 1.1 of the Code, along with Principles 1 and 3.

Complaint 1(b): Study by Daley-Yates et al, 2021, is not clinically meaningful in relation to supporting the claims of clinical superiority. Comments in the video are unbalanced and misleading.

The Committee noted that intercompany dialogue had occurred regarding the video, and understands as a result, GSK had withdrawn the video. It appeared that what remained unresolved as between GSK and Chiesi was Chiesi's request that GSK make a commitment to not use claims based on the 7-day pharmacology study.

First, the Committee discussed whether it should adjudicate on this matter in circumstances where GSK alleged that the matter of the video had been resolved through intercompany dialogue (and by it ceasing use of the video) and should therefore not be considered by the Committee.

The Committee determined that the Code does not prohibit the Committee from considering a matter where one company wishes the Committee to adjudicate and another does not. Relevantly, while the terms of section 16.1 of the Code state that Medicines Australia will not "accept" a complaint unless it has been the subject of intercompany dialogue which has not resolved, it does not expressly preclude or prohibit the Committee from dealing with a complaint in circumstances where no consensus view has been reached the parties about resolution of the complaint.

Similarly, the Committee was of the opinion that withdrawal of controversial material does not always resolve a matter. Consideration should be given to the length of time the material was in circulation, the volume of the audience, and any impact that material may have had on prescribers, as well as the severity of the alleged non-compliance.

In this circumstance, there remained one aspect of the complaint that had not been resolved during the intercompany dialogue process; that being a resolution to refrain from using the pharmacology study to support claims of clinical superiority. As such, the Committee determined that it was appropriate for it to consider the complaint regarding the video. However, the Committee considered that it should consider only the part of the complaint that remained in issue between the parties, namely, whether GSK could use the 7-day pharmacology study as a reference to promotional claims in future materials.

The 7-day Daley-Yates 2021 Study was then discussed. The Committee noted that whilst it may be scientifically valid, have scientific and potential clinical merit, it remained a short-duration pharmacological study that did not examine accepted clinical endpoints and as such, would preclude an ability to substantiate claims that infer efficacy or superiority. However the Committee was not of the view that the study could not be used at all in the future. The appropriateness of the use of the study would depend upon how it was used, including its context. In those circumstances the Committee formed a unanimous view that it was not appropriate for it to assess a 'hypothetical' future use and determined that there was no breach of the Code.

CONSIDERATION OF THE COMPLAINT continued ...

The Committee wishes to make it clear to companies that where intercompany dialogue has occurred, minutes should be taken which are then ideally agreed to by both parties. In any case (consensus minutes achieved or otherwise), these records should include a clear and concise articulation of what has been resolved, and what has not. Only in the case where a company is of the view that the matter has not been resolved after intercompany dialogue, would the Committee usually adjudicate. In this particular case, it was not clear on the face of the material before the Committee that a resolution had been reached during intercompany dialogue to the satisfaction of both parties, and therefore the Committee determined to hear the matter.

Complaint 2: Abuse of the Code and misuse of the complaints process by pursuing a series of frivolous and vexatious promotional challenges.

The Committee noted that the content and circumstances of the GSK complaints (which Chiesi complained breached sections 16.1 and 16.4 of the Code) was not before the Committee. Relevantly, Chiesi had declined to have the Committee determine those complaints, which it was entitled to do as a non-member company. It was therefore not appropriate for Committee to determine, for example, whether the content of those complaints was accurate (or the circumstances of the complaints being made) which would be relevant to a submission that they were made vexatiously.

With respect to Chiesi's complaint that the timing of the GSK complaints was intended to disrupt its business activities, the Committee did not consider that the material provided to it in this complaint was sufficient to substantiate that allegation on the balance of probabilities.

The Committee made a unanimous decision that no breach had occurred with regards to Section 16.4.

The Committee also rejected the allegation made by Chiesi in relation to a previous complaint #1164 that "*Medicines Australia elected not to adjudicate the complaint, but instead requested that GSK initiate intercompany dialogue with Chiesi*". Chiesi had been invited to have the complaint adjudicated by the Committee and had declined to have the Committee do so.

The Committee emphasised that the Code complaints process provided a fair and balanced mechanism to adjudicate disputes. In circumstances where a company has declined the opportunity to have the Code Committee adjudicate on the merits of a complaint, it would not in the usual course be appropriate for that company to then seek to use a separate complaints process to raise a complaint of this nature.

The Committee also considered whether a breach of section 16.1 of the Code had occurred, as Chiesi suggested, by reason of GSK making a complaint about matters resolved in intercompany dialogue. The Committee reiterated that the GSK complaints were not before it, and therefore it was not appropriate for the Committee to determine what had, or had not, been resolved in those complaints before they were submitted to Medicines Australia. In any event, the Committee identified that section 16.1 of the Code does not provide for a company to "breach" that section by submitting a complaint purportedly resolved through intercompany dialogue. Rather, section 16.1 is a procedural provision which provides that Medicines Australia will not accept a complaint unless it has been the subject of such dialogue (as discussed above).

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