Medicines Australia Code of Conduct Quarterly Report April – June 2019

The quarterly report of determinations of the Medicines Australia Code of Conduct and Appeals Committees

The Medicines Australia Code of Conduct was introduced in 1960 and is currently operating under Edition 18 (effective 16 May 2015).

This report covers all complaints finalised between April to June 2019. Complaints finalised during this period were in relation to materials or activities conducted under Edition 18 of the Code.

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.

Quarterly Reports preceding this Report are available from the Medicines Australia website: http://medicinesaustralia.com.au/code-of-conduct/code-of-conduct-reports/

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How do I obtain a copy of the Code?

Copies of Edition 18 of the Code (effective from 16 May 2015) and the Guidelines that accompany the Code are available from the website (http://medicinesaustralia.com.au/code-of-conduct/code-of-conduct-current-edition/)

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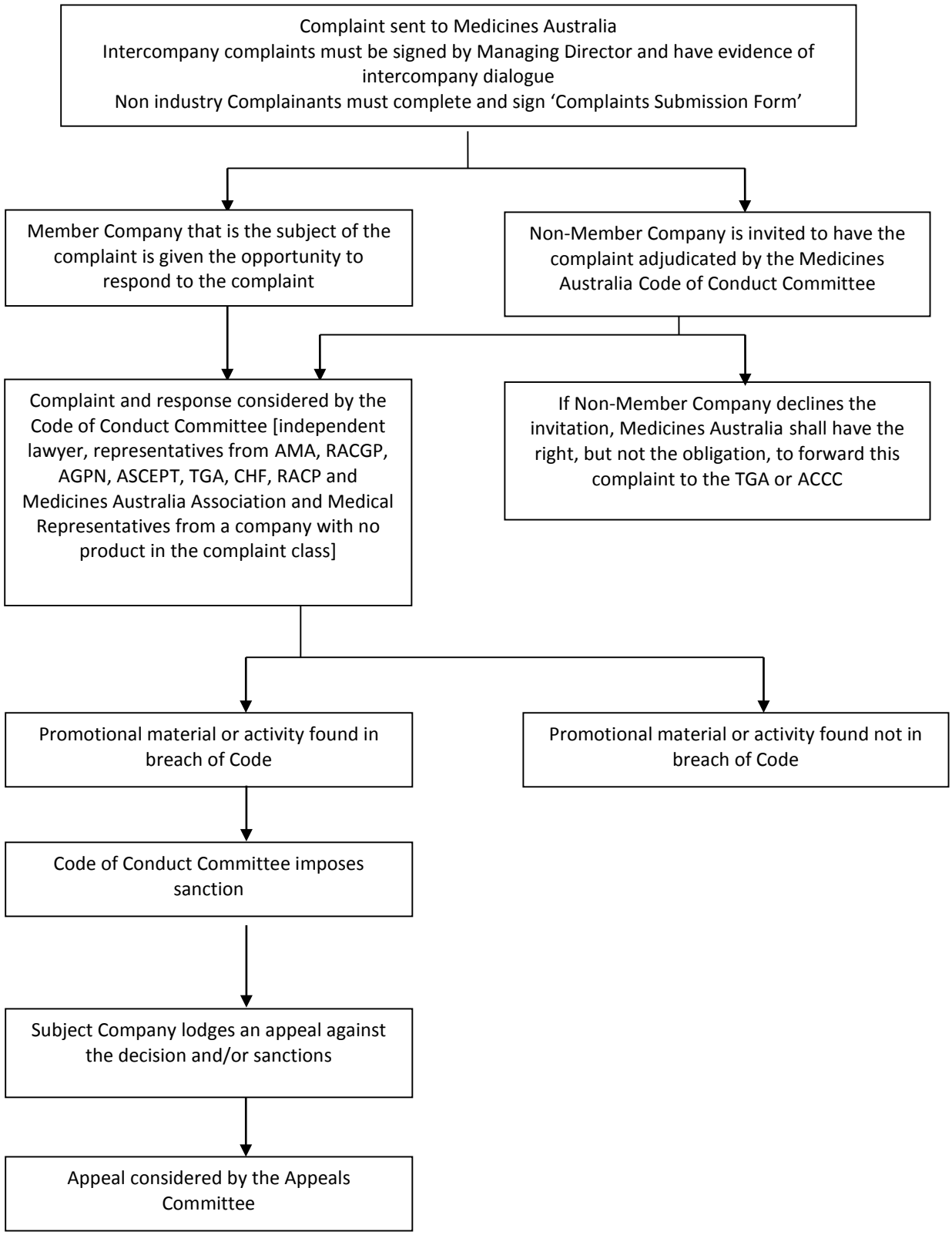
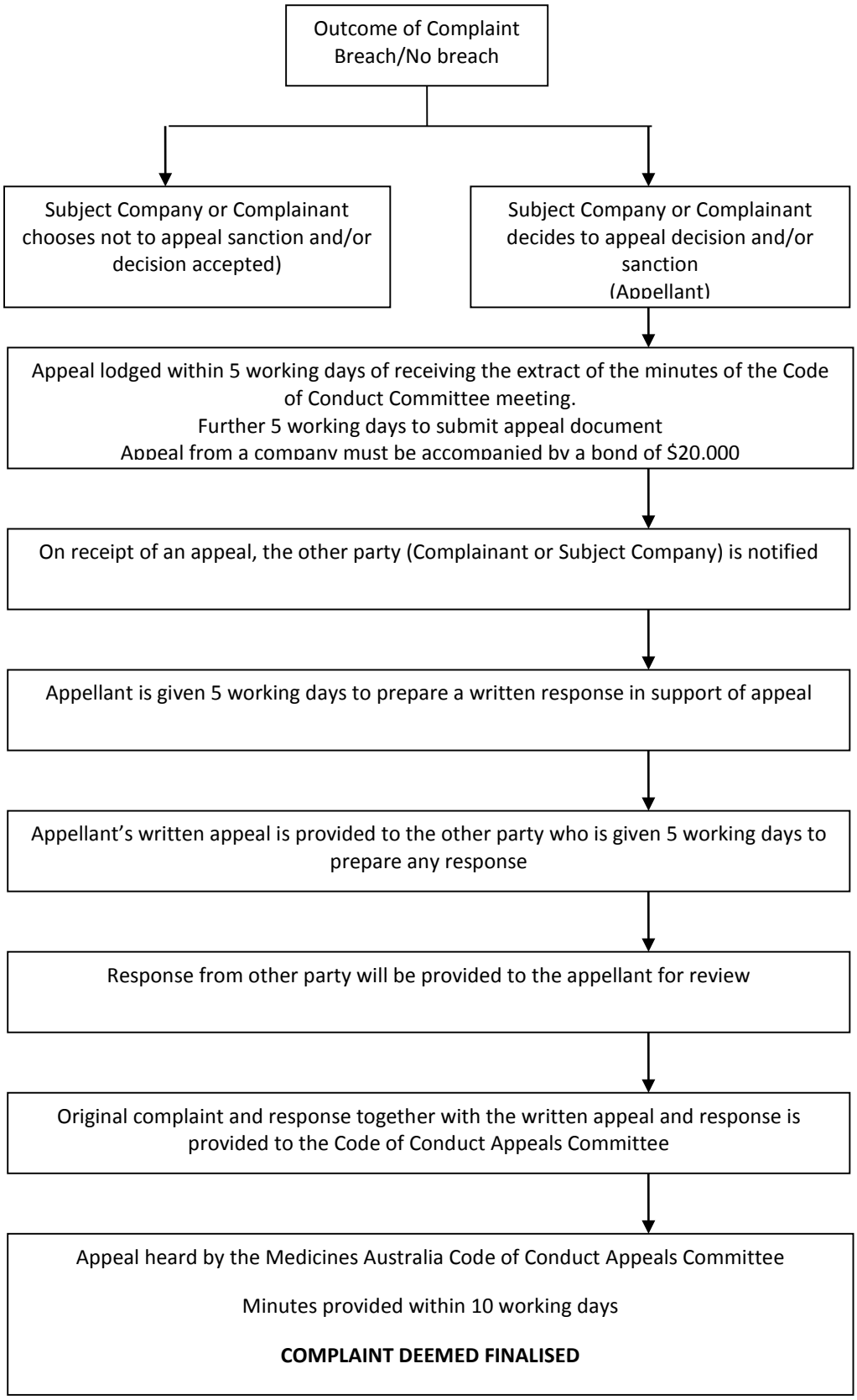
Medicines Australia Code of Conduct Complaints Handling Process



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

Medicines Australia Code of Conduct Appeals Committee Procedures



Committees and Secretariat

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.

Committee Member Biographies

Brief biographies for all Code, Appeals and Monitoring Committee members are available on the Medicines Australia website https://medicinesaustralia.com.au/code-of-conduct/committee-membership/

Code of Conduct Committee

Full Members (Voting rights)

- Independent Lawyer (Chairman) selected from a panel of up to 4 trade practices lawyers

Representatives nominated by:

- Australian General Practice Network (AGPN)
- Australian Medical Association (AMA)
- Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT)
- Consumers Health Forum of Australia (CHF)
- Royal Australasian College of Physicians (RACP)
- Royal Australian College of General Practitioners (RACGP)
- Medicines Australia Association Representatives (maximum 3)
- Medicines Australia Medical/Scientific Directors (maximum 2)

Observers (No voting rights)

- Therapeutic Goods Administration (TGA)
- Medicines Australia member companies' employees (maximum 2)
- Observer nominated by Medicines Australia (maximum 1)

Advisors (No voting rights)

- Secretary, Code of Conduct Committee
- Medicines Australia Chief Executive Officer or delegate
- Medicines Australia officer responsible for Scientific and Technical Affairs

Appeals Committee

Full Members (Voting rights)

- Independent Lawyer (Chairman) selected from a panel of up to 4 trade practices lawyers

Representatives nominated by:

- The College and/or Society associated with the therapeutic class of the product subject to appeal
- The target audience to which the activity was directed eg: AMA, RACGP
- Consumers Health Forum of Australia (CHF)
- Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT)
- Medicines Australia Association Representatives (maximum 2)
- Medicines Australia Medical/Scientific Director (maximum 1)

Advisors (No voting rights)

- Secretary, Code of Conduct Committee
- Medicines Australia Chief Executive Officer or delegate

Sanctions that can be imposed by the Code of Conduct Committee

Sanctions

If the Code of Conduct Committee finds a breach of the Code it may impose a sanction on the company found in breach. In order to determine an appropriate sanction the Committee will refer to the "Guidelines for determining Code sanctions" which are available on the Medicines Australia website. The following sanctions may be imposed:

Withdrawal of material or activity

Where promotional material or activity is found in breach of the Code the Committee will always require the company to cease use of the item or cease undertaking the activity.

Corrective letter

The Code of Conduct Committee will determine the audience for the letter based on the original distribution of the material found in breach of the Code.

Corrective advertisement

A corrective advertisement must be placed in the same publication as that found in breach of the Code.

Fines (applicable under Edition 18 of the Code)

Breach	Fine
Technical breach Minor breach	Maximum of $100,000
Moderate	Maximum of $150,000
Severe breach	Maximum of $200,000
Severe breach where activities completed Repeat of previous breach	Maximum of $250,000
Cumulative fine for multiple breaches	Maximum of $300,000
Failure to complete corrective action in 30 calendar days Failure to pay a fine in 30 calendar days	Maximum of $50,000
Abuse of the Code (in accordance with Section 25)	Maximum of $200,000

Table of finalised complaints April – June 2019

No.	Subject Company	Material or Activity	Product	Complainant	Outcomes	Sanction
1150	AstraZeneca Pty Ltd	Promotional material	Symbicort	GlaxoSmithKline Australia Pty Ltd	Breach 1.1, 1.2,1.2.2, 1.3, 1.4	Fine $60,000 and corrective letter to HCPs
1151	CSL Behring Pty Ltd	Market research	Not applicable	Healthcare professional	No breach	Not applicable
1152	Merck Sharp & Dohme Australia Pty Ltd	Promotional materials	Keytruda	Novartis Pharmaceuticals Australia Pty Limited	No breach	Not applicable

1150 – Symbicort™ Promotional Material

Subject Company: AstraZeneca Pty Ltd

Complainant: GlaxoSmithKline Australia Pty Ltd (GSK)

Product: Symbicort™

Complaint
GSK alleged that promotional materials for Symbicort using the claim "Symbicort maintenance and anti-inflammatory reliever therapy" promote an unapproved use of Symbicort. Further it alleged that the claim is false and misleading because it is unsubstantiated, unreferenced and is not consistent with the body of evidence. GSK alleged that AstraZeneca had failed to meet its responsibility to ensure that the claim is consistent with the body of evidence.

The complaint also related to a qualifying statement "Symbicort maintenance and anti-inflammatory reliever therapy vs fixed dose Seretide and SABA" which was referenced to a study by Kuna et al. GSK alleged that the qualifying statement is misleading, incorrect and unsubstantiated because the referenced study compared Symbicort maintenance and reliever therapy vs Seretide and did not evaluate Symbicort's effect on airway inflammation.

Sections of the Code
The claims were alleged to be in breach of the following Sections of Edition 18 of the Code:

- Section 1.1 Responsibility
- Section 1.2 Substantiating Data
- Section 1.3 False or Misleading Claims
- Section 1.4 Unapproved indication

Response
In its response to the complaint, AstraZeneca denied any breach of the Code. AstraZeneca stated that Symbicort is approved for the treatment of asthma and COPD and has two dosing regimens: as maintenance and reliever therapy and as maintenance therapy. As Symbicort is a combination therapy containing budesonide, AstraZeneca states that the anti-inflammatory effect of budesonide applies regardless of the dosing regimen.

AstraZeneca denied it had breached any section of the Code. It stated that the promotional material is within the approved dosing regimen for Symbicort and that there is a body of evidence to support the effectiveness and anti-inflammatory effects of the product.

Further to responding to the complaint, AstraZeneca alleged that GSK has not properly followed the inter-company dialogue process, had made allegations of breach of the Code that were unfounded and which misrepresented referenced studies. AstraZeneca alleged that GSK was in breach of Section 27 Abuse of the Code for making a frivolous and vexatious complaint.

Code of Conduct Committee decision
The Code of Conduct Committee made the following decisions in relation to the claims in the promotional material:

Claim 1*: "Consider Symbicort maintenance and anti-inflammatory reliever therapy,[t] in place of SABA, for relief as required to treat her asthma*
[t]Symbicort maintenance and anti-inflammatory reliever therapy is recommended with Symbicort Rapihaler 50/3 or 100/3 OR Turbuhaler 100/6 or 200/6"

The Committee decided by majority that the claim was in breach of Sections 1.1, 1.2.2, 1.3 and 1.4 of the Code.

Claim 2: *"*Symbicort maintenance and anti-inflammatory reliever therapy vs fixed dose Seretide + SABA"*

The Committee decided by majority that the claim was in breach of Sections 1.1, 1.2 and 1.3 of the Code.

Alleged breach of Section 27 – Abuse of the Code

The Committee formed a unanimous view that the complaint did not contravene Section 27 of the Code. The complaint was not frivolous or vexatious and GSK should not be required to respond to the allegation.

Sanctions

The Code of Conduct Committee determined that the breaches constituted moderate breaches of the Code and imposed the following sanctions:

- Noting that the promotional material had already been withdrawn from use, the claims found in breach must not be used again in the same or similar form;
- In a majority decision the Committee imposed a fine of $60,000;
- In a majority decision, the Committee determined a corrective letter should be required to be sent to all healthcare professionals who had received the promotional item containing the claims, such contravention letter to be approved in advance.

Consideration of the complaint

The Chairman provided a brief summary of the complaint.

The Committee considered the complaint by discussing each of the two claims and the alleged breaches in turn.

Claim 1

Consider Symbicort maintenance and anti-inflammatory reliever therapy,[t] in place of SABA, for relief as required to treat her asthma

[t]Symbicort maintenance and anti-inflammatory reliever therapy is recommended with Symbicort Rapihaler 50/3 or 100/3 OR Turbuhaler 100/6 or 200/6.

The Committee noted that the primary issue subject to complaint was the phrase "anti-inflammatory reliever therapy". The claim appeared in a promotional item relating to management of asthma in patients with allergic rhinitis.

The Committee noted that the phrase "anti-inflammatory reliever" was not used in the Symbicort Product Information under *Therapeutic indications* (or anywhere else in that document). The indications for the treatment of asthma are "Symbicort maintenance and reliever therapy" and "Symbicort maintenance therapy". The phrase "maintenance and reliever therapy", referring to the combination of an inhaled corticosteroid (budesonide) and a long-acting beta-agonist bronchodilator (formoterol), has been in use for many years. There was no dispute about the efficacy of the combination inhaler as a maintenance and reliever therapy, which is well-supported by published evidence and the Product Information.

With regard to the claim "anti-inflammatory reliever", the Committee noted that whilst inhaled budesonide has an anti-inflammatory action in the airways, there was no evidence that this anti-inflammatory action was the mechanism that enabled the combination inhaler (with formoterol) to be used as a reliever therapy.

The claim containing the phrase "anti-inflammatory reliever" recommends using Symbicort in place of a short-acting beta-agonist (SABA) for relief of asthma exacerbations. Immediate relief of asthma symptoms requires bronchodilation within several minutes, whereas the anti-inflammatory effects of budesonide, according to the Product Information, may take much longer, up to several hours. The Committee was unable to identify any evidence to support the claim that Symbicort is an "anti-inflammatory reliever" because of the anti-inflammatory effect of budesonide.

The Committee discussed the evidence presented by AstraZeneca in support of the "anti-inflammatory reliever" claim. It was noted that the studies presented in the response, including the literature review presented by AstraZeneca, support that budesonide has an anti-inflammatory effect. However, the time course for the anti-inflammatory effects do not support the "anti-inflammatory reliever" use of Symbicort.

Acute bronchoconstriction in asthma, as already noted, requires relief within two to three minutes. None of the papers referenced by AstraZeneca in its response to the complaint used the term "anti-inflammatory reliever" or "anti-inflammatory reliever therapy". Further, the studies by O'Byrne *et al* (2005) and Vogelmeier *et al* (2005), to which the full claim containing "anti-inflammatory reliever" is referenced, do not use that term.

The Committee also noted the scope of the evidence presented by AstraZeneca and their general limitations (as to size and participants) as further relevant to the issue of whether the claims made in the promotional material were substantiated.

The Committee noted that it appeared that AstraZeneca has conducted further studies to support the use of Symbicort as an anti-inflammatory reliever therapy in mild asthma in place of short-acting reliever inhalers, as reported in a global AstraZeneca media release in May 2018. The Committee noted that the media release had not been published in Australia and therefore was not relevant to the complaint concerning the promotional material for Australian healthcare professionals. In any event, the existence of a media release alone would not itself be sufficient to substantiate any claim made in promotional material.

A majority of the Committee considered that "Symbicort maintenance and anti-inflammatory reliever therapy" was not consistent with the current approved indications for Symbicort. There was an alternative interpretation from one Committee member, who considered that the claim was consistent with the approved indications for Symbicort. The member thought that the combination inhaler does have an anti-inflammatory mechanism of action and it can be used for both maintenance and reliever therapy, according to the approved indications. The member further considered that the claim was not promoting Symbicort as a reliever therapy alone, only its use as a reliever for acute exacerbations whilst using Symbicort for maintenance treatment. However, the member accepted that there is no proven mechanism for the reliever effect.

The Committee also considered the phrase "anti-inflammatory reliever" in context of the full claim: "Consider Symbicort maintenance and anti-inflammatory reliever therapy, in place of SABA, for relief as required to treat her asthma" which, in the Committee's view, was promoting the use of Symbicort as a reliever inhaler. In particular, the Committee referred to the phrase "for relief as required" as suggesting fast acting relief (i.e. for a flare up). The Committee noted that during inter-company dialogue, AstraZeneca had proposed to change the wording of the claim to "Consider Symbicort maintenance and anti-inflammatory reliever therapy, in place of maintenance plus separate SABA". However, the approved indications for Symbicort for asthma are that it is indicated for patients where a combination inhaled corticosteroid (ICS) and long-acting beta2 agonist (LABA) is appropriate, including patients symptomatic on ICS therapy, and patients established on regular LABA and ICS therapy. The Committee remained concerned that the claim "anti-inflammatory reliever therapy, in place of SABA" was promoting the use of Symbicort beyond its approved indications, despite the changed wording of the claim agreed during inter-company dialogue.

The Committee also noted the use of the word "recommended" in the second iteration of claim 1 as potentially suggesting the indication was approved in some way by a third party such as the Therapeutic Goods Administration, when that was not the case. This was further emphasised given that the promotional material cited the phrase under the heading "Recommendation", which appeared in a large font.

The Committee concluded by majority decision that claim 1 "Consider Symbicort maintenance and anti-inflammatory reliever therapy, in place of SABA, for relief as required to treat her asthma" and "anti-inflammatory reliever therapy" was in breach of the following sections of the Code:

- Section 1.1: the content of the promotional material was not fully supported by the Product Information, literature or 'data on file' or appropriate industry source (where these do not conflict with the Product Information). The Committee noted that the terms of Section 1.1 of the Code provide that it is "*fundamental that any claim made must be consistent with the Australian Product Information document, irrespective of the source on which the claim is based*";
- Section 1.3: the claims as phrased were misleading to healthcare professionals, noting that section 1.3 of the Code provides that all information and claims "*must not mislead either directly, by implication or by omission"*; and
- Section 1.4: the claim involved a promotion of an indication not approved for registration in Australia by the Therapeutic Goods Administration.

The Committee also concluded by majority decision that the claim was in breach of Section 1.2.2 of the Code because it could not be adequately substantiated.

Claim 2

**Symbicort maintenance and anti-inflammatory reliever therapy vs fixed dose Seretide + SABA*

The Committee discussed the second claim subject to complaint, which appeared in the promotional material as a qualifying statement to the claim "39% reduction in flare-ups with a 25% lower mean ICS dose vs. Seretide". This claim was referenced to a study by Kuna P et al (2007) and linked to claim 2 by an asterisk. The second claim also included the words "anti-inflammatory reliever therapy".

The Committee considered the Kuna et al study, which evaluated the efficacy of the Symbicort maintenance and reliever therapy (SMART) versus a fixed dose of Seretide with a SABA (terbutaline) as needed and versus a fixed dose of Symbicort with a SABA (terbutaline) as needed. Whilst the study showed that the SMART reduced flare-ups, the study did not evaluate Symbicort as an "anti-inflammatory reliever" and this term was not used in the Kuna et al study. Whilst the study supported the reduction in flare-ups presented graphically in the promotional material, the reason for this effect was not explored in the study. The authors note that the reason for the reduction in exacerbations is yet to be fully elucidated. The Committee confirmed its view that there were no data presented that the reliever effect is due to the anti-inflammatory effect of budesonide in Symbicort.

The Committee found by majority decision that the second claim subject to complaint was in breach of Sections 1.1, 1.2 and 1.3 of the Code.

Sanctions

Having found that the claims were in breach of the Code, the Committee considered appropriate sanctions.

The Committee discussed the severity of the breaches. The Committee was particularly concerned at the risk of a doctor prescribing Symbicort, at the strengths used for the maintenance and reliever regimen, for a patient in place of a SABA reliever for acute exacerbations. The Committee determined that the breaches were in the moderate category. There were no apparent safety implications for patients arising from the claims but there would be an effect on how the medical profession would prescribe the product.

The Committee determined that the following sanctions should be imposed:

- Noting that the promotional material had already been withdrawn from use, the claims found in breach must not be used again in the same or similar form;
- In a majority decision the Committee imposed a fine of $60,000;
- In a majority decision, the Committee determined that a corrective letter should be required to be sent to all healthcare professionals who had received the promotional item containing the claims found in breach, such corrective letter to be approved in advance.

Allegation of a breach of Section 27 of the Code by GSK

In its response to the complaint, AstraZeneca had alleged that GSK had not properly followed the inter-company dialogue process. It alleged that GSK had made allegations of breach of the Code that were not raised during inter-company dialogue and had included in its complaint to Medicines Australia issues that had been resolved during the inter-company dialogue. AstraZeneca also alleged that GSK had relied on four selectively chosen studies, which had not been provided to it during inter-company dialogue. AstraZeneca alleged that GSK had made a frivolous and vexatious complaint and was in breach of Section 27 – Abuse of the Code.

The Committee considered that the issues raised in the complaint in relation to claim 2 were substantially the same as claim 1, which primarily related to the claim "anti-inflammatory reliever therapy". Whilst some matters had been resolved during inter-company dialogue, the use of this phrase in a claim for Symbicort had not been resolved.

The Committee concluded that, having found each claim in breach of the Code, the complaint had not been frivolous or vexatious. Whilst the inter-company dialogue process could have been improved (including by providing AstraZeneca with copies of the studies GSK relied on in advance), the complaint did not rise to the level of being frivolous or vexatious. The Committee formed a unanimous view that the complaint would not be considered frivolous or vexatious and there was no breach of Section 27, such that and GSK should not be required to respond to this allegation.

Appeal

AstraZeneca submitted an appeal against the decisions of the Code of Conduct Committee. AstraZeneca denied that the Symbicort promotional claims were in breach of the Code.

AstraZeneca argued that the claims containing the words "maintenance and anti-inflammatory reliever" were not designed to promote Symbicort except in accordance with the product's registration and approved Product Information. AstraZeneca stated that the term "anti-inflammatory reliever" merely describes the product as a fixed-dose combination of an inhaled corticosteroid (the anti-inflammatory component) and a fast-acting beta agonist (the reliever component).

AstraZeneca asserted that the Code does not require a claim to be taken verbatim from the PI, as long as claims are consistent with the body of evidence and do not conflict with the PI. The inclusion of the term "anti-inflammatory", as an adjective to describe and differentiate the as-needed reliever component of the "Symbicort maintenance and reliever therapy" regimen, is consistent with the approved PI.

Response to the appeal

GSK did not accept the arguments presented by AstraZeneca in its appeal and stated that it considered that the Code of Conduct Committee was correct in its findings.

GSK argued that the Code Committee's decisions were not based on the fact that the specific wording "anti-inflammatory reliever" is not used in the Symbicort Product Information. The Code Committee had assessed the implications of the claims, the meaning of "anti-inflammatory reliever" and the available body of evidence in finding that the claims were in breach of the Code.

GSK asserted that AstraZeneca had changed the nomenclature to "Symbicort maintenance and anti-inflammatory reliever therapy" at the same time as its development of the use of Symbicort as required (PRN) regimen in mild asthma. This usage is not approved in Australia at the time of publication of the material. Therefore, GSK asserted, the claims subject to the complaint constituted pre-license promotion of Symbicort for the treatment of asthma in a 'PRN' dosing regimen.

GSK referred to the claim "Consider Symbicort maintenance and anti-inflammatory reliever therapy, in place of SABA, for relief as required to treat her asthma". The current

approved indication for Symbicort maintenance and reliever therapy requires patients to be on existing ICS-based regimen, and not in place of SABA, for relief as required. Therefore, GSK asserted that the claim is in breach of the Code.

Appeals Committee decision

Claim 1

The appeal by AstraZeneca against the findings of the Code of Conduct Committee was not upheld. The Appeals Committee unanimously confirmed that the claim was in breach of Sections 1.1, 1.2.2, 1.3 and 1.4 of the Code.

Claim 2

The appeal by AstraZeneca against the findings of the Code of Conduct Committee was not upheld. The Appeals Committee unanimously confirmed that the claim and was in breach of Sections 1.1, 1.2 and 1.3 of the Code.

Sanctions

The Appeals Committee determined that the sanctions imposed by the Code of Conduct Committee should remain unchanged; that is, the Appeals Committee confirmed:

- The claims found in breach must not be used again in the same or similar form
- A fine of $60,000 should be imposed
- A corrective letter should be required to be sent to all healthcare professionals who had received the promotional item containing the claims.

The Appeals Committee determined that the appeal bond of $20,000 should be retained by Medicines Australia.

Consideration of the Appeal

Personnel from AstraZeneca and GSK attended the meeting and gave presentations to the Appeals Committee.

The Chairman explained the process for consideration of an appeal. The Appeals Committee must be persuaded that the findings of the Code of Conduct Committee (Code Committee) involved an error on the basis of which the decisions of the Code Committee should be set aside or varied.

The Chairman invited AstraZeneca to give their appeal presentation. The following summarises that presentation and discussion with the Appeals Committee.

- AstraZeneca considers that the Code Committee had misunderstood the pharmacology of Symbicort and its two components and the Symbicort "maintenance and anti-inflammatory reliever" regimen. The nomenclature of this regimen is the pivotal issue in the Code Committee's findings and was the only issue that remained in dispute following inter-company dialogue with GSK.
- AstraZeneca argued that Symbicort promotional material and the two claims subject to complaint only promote the "Symbicort maintenance and anti-inflammatory reliever" regimen, which is consistent with the approved Product Information (PI).
- AstraZeneca gave an overview of asthma, which is a chronic inflammatory disease characterised by exacerbations and worsening inflammation, causing narrowing of the airways. There are two forms of reliever used in addition to maintenance and preventer treatments – short-acting beta-2 agonists (SABA) and an inhaled corticosteroid combined with a rapid and long-acting beta-2 agonist (ICS/LABA combination). Only Symbicort (containing the ICS budesonide and LABA formoterol) and other generic brands are approved in Australia for use as both maintenance and a reliever therapy.
- Budesonide is an anti-inflammatory ICS. AstraZeneca does not claim that the ICS component enables Symbicort to be used as a reliever. The LABA formoterol provides the reliever effect.
- AstraZeneca considers it is essential for prescribers to understand that there is a difference between relievers. Patients using Symbicort for maintenance therapy and as a reliever for asthma exacerbations will receive an anti-inflammatory ICS.
- AstraZeneca referred to the National Asthma Council *Australian Asthma Handbook* (June 2019), which states that dispensing three or more SABA inhalers in

a year increases risk of flare-ups and dispensing more than twelve SABA inhalers in a year increases the risk of asthma deaths. The clinical evidence of increased risk of adverse clinical outcomes associated with increased SABA use was available when the promotional material was published (August 2018).

- AstraZeneca presented a graph representing studies of various treatment regimens which compared the Symbicort maintenance and reliever regimen with ICS + SABA, a different ICS/LABA combination + SABA and Symbicort + SABA. AstraZeneca stated that the studies showed superior efficacy (less exacerbations) from the Symbicort used for both maintenance and reliever. AstraZeneca stated that this is supported by a 2013 Cochrane review and a 2010 meta-analysis of six trials using the Symbicort maintenance and reliever regimen, which highlighted that the superior efficacy was due to the budesonide delivered when Symbicort is used as a reliever.
- AstraZeneca asserted that it does not claim that the anti-inflammatory action of budesonide enables Symbicort to be used as a reliever. The LABA formoterol provides the reliever effect of bronchodilation. However, AstraZeneca believes that the clinical evidence supports classifying Symbicort as an "anti-inflammatory reliever" because the two components provide anti-inflammatory effects (budesonide) and relief of bronchoconstriction (formoterol).
- AstraZeneca contended that the Code Committee had misunderstood the clinical pharmacology of Symbicort. The LABA formoterol has a fast onset of action (1 – 3 minutes), which is why it is used as a reliever. AstraZeneca does not claim that budesonide is responsible for the reliever mechanism of action. When the combination of formoterol and budesonide in Symbicort is taken as a reliever, patients also get the anti-inflammatory effect. The use of Symbicort for both maintenance and reliever therapy has been shown to be clinically superior to use of a SABA as a reliever.
- AstraZeneca presented results from a study by Rabe KF et al. (2006), which is included in the Symbicort PI, as part of the clinical evidence for the superiority of the Symbicort maintenance and reliever regimen versus either formoterol or terbutaline as relievers. AstraZeneca contended that this study demonstrates that both the budesonide and formoterol components contribute to improved asthma control.
- A member of the Appeals Committee questioned why there had been a change in 2019 to use the term "anti-inflammatory reliever" if the data had been available since at least 2006. AstraZeneca responded that it had been a significant change to recognise Symbicort as a reliever regimen and that no separate SABA reliever was required. In addition, understanding has evolved significantly over time from initial use of ICS with a separate bronchodilator reliever. Patients need to understand that asthma is an inflammatory disease which is the foundation of treatment with ICS.
- AstraZeneca contended that the Code Committee made an error in finding that the claim and term "anti-inflammatory reliever" was in breach of Code of Conduct Section 1.1. The Code does not require that a claim is the exact or verbatim wording from the PI. The claims were consistent with and fully supported by the Symbicort PI.
- AstraZeneca referred to the revised wording of the claim, discussed during inter-company dialogue, which was raised as a concern by the Code Committee. AstraZeneca contended that this also indicated that the Code Committee had misunderstood the Symbicort maintenance and "anti-inflammatory reliever" regimen. The proposed alternative claim, except for the term "anti-inflammatory reliever", had been accepted by GSK during the inter-company dialogue and is fully in line with the PI.
- With regard to Claim 2, AstraZeneca reiterated that it was not claiming that

budesonide is the reliever component of Symbicort. It maintained that the term "anti-inflammatory reliever" is appropriate. Although the Kuna P et al. study did not use the term "anti-inflammatory reliever", it does support that the increased ICS dose when Symbicort is used as a reliever "was the defining feature of Symbicort maintenance and reliever therapy".

- AstraZeneca argued that the Code Committee had misunderstood the Symbicort maintenance and reliever regimen and therefore had been concerned that doctors might prescribe Symbicort for acute asthma exacerbations, as a reliever. AstraZeneca had not promoted Symbicort without the daily maintenance therapy; only that there was no need for an additional SABA reliever.
- AstraZeneca asserted that GSK's Annexure B to its complaint was incomplete, did not represent the body of evidence, had selectively included some of the outcomes from included studies, had misrepresented objectives, results and outcomes of included studies and had ignored the authors' conclusions. AstraZeneca argued that Annexure B should be disregarded by the Appeals Committee.
- AstraZeneca concluded, stating that Symbicort has an anti-inflammatory and reliever mechanism. The claims were not promoting Symbicort as an "anti-inflammatory reliever" alone, only as a reliever for acute exacerbations when also using Symbicort maintenance therapy. AstraZeneca asserted that it is crucial to differentiate between different reliever options. Symbicort includes budesonide, an anti-inflammatory ICS, whereas SABAs are not anti-inflammatory, which is the reason for using the term "anti-inflammatory reliever".
- AstraZeneca stated that both claims 1 and 2 were fully supported by, and consistent with, the PI and the approved indication; were not misleading; could be fully substantiated and were, therefore, not in breach of Sections 1.1, 1.2, 1.3 or 1.4 of the Code.

The Chairman thanked the AstraZeneca representatives for their presentation and invited the GSK representatives to make their presentation to the Appeals Committee. The following summarises that presentation and discussion with the Appeals Committee.

- GSK asserted that AstraZeneca has argued that the complaint is only about the use of an adjective "anti-inflammatory". However, the word is part of a promotional claim which is not consistent with the approved PI. Considering the claim as a whole, it promotes an unapproved indication.
- GSK considered that the Code Committee was correct in its assessment of the evidence and its findings and its analysis of AstraZeneca's arguments. GSK requested the Appeals Committee to confirm the Code Committee's findings.
- GSK asserted that it is nonsensical to debate whether the term "anti-inflammatory" was used merely as an adjective. AstraZeneca has acknowledged that Claim 1, as a whole, is a promotional claim: "Consider Symbicort maintenance and anti-inflammatory reliever therapy, in place of SABA, for relief as required to treat her asthma". The claim promotes Symbicort as a reliever instead of SABA for the treatment of asthma. The claim cannot be substantiated and is false and misleading and was found in breach by the Code Committee.
- GSK questioned why AstraZeneca had changed the term "Symbicort maintenance and reliever therapy" or SMART, which has been in use for 15 years in scientific publications and literature, to include "anti-inflammatory reliever".
- GSK argued that none of the references presented by AstraZeneca in its appeal presentation refer to "anti-inflammatory reliever therapy" for Symbicort.
- AstraZeneca had referred to the *Australian Asthma Handbook* as the rationale for the recommendation, but neither the Handbook nor the Symbicort PI use the nomenclature "anti-inflammatory reliever". The Handbook

continues to use the term "maintenance and reliever therapy", including in its most recent update. Similarly, the Global Initiative for Asthma Guidelines 2019 continue to refer to ICS plus formoterol as a reliever, not an "anti-inflammatory reliever". GSK noted that the Symbicort PI does not use the term "anti-inflammatory reliever", in the therapeutic indications.

- GSK asserted that claim 1 was misleading, unsubstantiated, not supported by the PI and not supported by the literature. It was correct for the Code Committee to find the claim in breach of Section 1.1 of the Code.
- GSK argued that the issue was not about whether inhaled corticosteroids have an anti-inflammatory effect. "Anti-inflammatory reliever" is a claim that promotes Symbicort as rapidly relieving inflammation associated with asthma symptom flare-up. Readers would associate the word "reliever" with rapid or immediate onset of effect. Scientific evidence does not support the claim of Symbicort being an "anti-inflammatory reliever".
- In relation to Claim 2, which is referenced to the Kuna P et al. study, GSK argued that this study did not compare Symbicort as an "anti-inflammatory reliever" versus Seretide plus SABA.
- GSK noted that the same "anti-inflammatory reliever" nomenclature had been included in the Minimum PI in the promotional material, which had been accepted as an error by AstraZeneca during inter-company dialogue. This is not part of the current complaint.
- GSK rejected AstraZeneca's criticisms of GSK's Annexure B analysis. The annexure summarised six studies of Symbicort maintenance and reliever therapy that had assessed the effect on inflammatory markers, because the claim is about inflammation. None of the 6 published studies used the term "Symbicort maintenance and anti-inflammatory reliever therapy" or "anti-inflammatory reliever".
- GSK referred to one study by Lin et al. (2015), comparing budesonide combined with formoterol at different doses versus terbutaline, which overall showed no significant effect on inflammatory markers in the acute phase (0 to 6 hours). Therefore, GSK asserted, AstraZeneca is not able to claim that Symbicort has an anti-inflammatory reliever effect. GSK considered that the Code Committee was correct in finding the claim in breach of Sections 1.2.2 and 1.3 of the Code.
- GSK referred to the approved indications for Symbicort, arguing that it is not approved for use as "an anti-inflammatory reliever therapy, in place of SABA, for relief as required…". GSK presented a comparison between an extract from an AstraZeneca global media release (May 2018) and claim 1, highlighting the similarity of wording. GSK asserted that the Code Committee was correct in finding the claim in breach of Section 1.4.
- GSK concluded that the Code Committee was correct in all its findings; there had been no errors by the Committee.
- The Appeals Committee asked GSK to further explain its rationale for arguing that the inclusion of "anti-inflammatory" makes the claim for an unapproved indication. GSK responded that the claim must be considered in its entirety. GSK argued that the product is not an "anti-inflammatory reliever" and it is not approved for use as a reliever in place of SABA. Whilst there had been agreement by AstraZeneca during inter-company dialogue to change the claim to refer to "in place of maintenance + SABA", GSK remained of the view that "anti-inflammatory reliever" is an unapproved use of Symbicort.
- AstraZeneca responded that ICS are anti-inflammatory. The claim is talking about using Symbicort as a reliever when on maintenance treatment and asthma exacerbations occur, which is consistent with the PI and approved indications. AstraZeneca did not accept that claims must be a verbatim transcription of the PI indications.
- GSK responded that the issue is about the conflation of the term "anti-inflammatory" with "reliever", which is not correct because ICS require hours to

have an effect on markers of inflammation.
- AstraZeneca reiterated that the Kuna et al. study showed that the defining feature of the maintenance and reliever regimen in reducing asthma flare-ups was ensuring increases in anti-inflammatory ICS doses, which is the budesonide component of Symbicort.
- The Appeals Committee asked AstraZeneca to explain its rationale for putting "anti-inflammatory" with "reliever", which is the basis of the complaint, rather than another construction. AstraZeneca responded that only Symbicort includes an anti-inflammatory ICS in conjunction with a fast-acting beta-2 agonist and can be used as a reliever therapy in asthma.

The Chairman thanked the GSK representatives for their presentation and asked AstraZeneca to give its short response.

AstraZeneca stated that the media release referring to the SYGMA studies is irrelevant to the complaint. GSK had referred to its expectations about AstraZeneca's future indications for Symbicort whereas the promotional piece only promotes Symbicort within its current approved indications. AstraZeneca cautioned the Committee about accepting GSK's interpretation of studies in its Annexure B and instead to review the actual papers.

AstraZeneca advised the Committee that it had already accepted the error in the Minimum PI in the piece during intercompany dialogue. This aspect is not relevant to the current complaint. Further, the use of the word "recommendation" in the piece was also resolved during intercompany dialogue; AstraZeneca has agreed to use an alternative wording that does not imply a recommendation from the Australian Asthma Handbook.

AstraZeneca concluded that the intention of the claims is to refer to the mode of action of the combination ICS + LABA inhaler.

In a final response to a question from the Committee, GSK stated that it has never proposed that claims must be a verbatim transcription of the indications or PI.

This concluded the company presentations and both parties were then excused from the hearing to allow the Appeals Committee to deliberate on the appeal.

The Appeals Committee discussed AstraZeneca's appeal and GSK's response to the appeal.

The Appeals Committee noted that there had been an evolution of asthma treatment since the LABA inhalers were approved in the 1990s, with salmeterol being the first LABA. As a consequence of clinical studies with LABAs, showing they do not have anti-inflammatory effects, LABAs are always combined with an ICS. Research led to the single maintenance and reliever therapy or SMART regimen, using a fixed dose inhaler combination of ICS and LABA.

The Appeals Committee noted that Symbicort contains two unrelated drugs that have different pharmacological mechanisms of action – budesonide is an anti-inflammatory ICS and formoterol is a long-acting beta-2 agonist which is a bronchodilator. The ICS component has an anti-inflammatory effect that has an onset of action of approximately 4 hours and effect duration of approximately 12 hours. The LABA reliever component has an onset of a few minutes, which is needed for immediate relief of symptoms.

The Appeals Committee agreed with the Code Committee's conclusion that the term "anti-inflammatory reliever" implies that the reliever component has anti-inflammatory properties, which it does not. Whilst there is evidence that the combination of ICS and LABA in Symbicort when used in the maintenance and reliever regimen results in a reduction in asthma exacerbations, there is no evidence supporting that this is due to an anti-inflammatory effect of the LABA component, which was confirmed by AstraZeneca in its appeal. The Appeals Committee unanimously agreed that the claim "anti-inflammatory

reliever" in relation to Symbicort could not be substantiated and was not consistent with the approved indications.

The Appeals Committee noted it was the conflation of "anti-inflammatory" with "reliever" that led to its conclusion that claims 1 and 2 were in breach of the Code. A future, different claim using the term "anti-inflammatory" that did not imply that the reliever has this effect might not lead to the same conclusion.

The Appeals Committee discussed the other element of claim 1 – "in place of SABA". The Appeals Committee agreed with the Code Committee that the claim might lead a prescriber to prescribe Symbicort outside its approved indications, as a reliever inhaler that can be used alone outside of maintenance and reliever therapy, instead of a SABA. The Appeals Committee agreed with the Code Committee that this was not consistent with the approved indications.

The Appeals Committee agreed with the Code Committee's evaluation that claim 2, referenced to the Kuna et al. study, misrepresented that study, which did not evaluate Symbicort as an "anti-inflammatory reliever".

The Appeals Committee determined that the Code Committee's reasons for finding both claims 1 and 2 in breach of the Code were appropriate and had not involved any error in reaching its decisions.

The Appeals Committee unanimously confirmed the Code Committee's decisions that Claim 1 was in breach of Sections 1.1, 1.2.2, 1.3 and 1.4 of the Code and that the appeal by AstraZeneca should not be upheld. The Appeals Committee also unanimously confirmed the Code Committee's decisions that Claim 2 was in breach of Sections 1.1, 1.2 and 1.3 of the Code and that the appeal by AstraZeneca should not be upheld.

The Appeals Committee discussed the sanctions imposed by the Code Committee. It agreed that the breaches were moderate, as evaluated by the Code Committee. The Appeals Committee unanimously determined that the sanctions imposed by the Code Committee should not be varied.

1151 Market Research

Subject Company: CSL Behring (Australia) Pty Ltd (CSL Behring)

Complainant: Healthcare professional (Clinical Nurse Consultant)

Product: Not applicable

Complaint
A clinical nurse consultant (CNC) alleged that CSL Behring had breached the Code of Conduct in relation to market research it had conducted. The complainant alleged that the company failed to make it clear to them that the market research was being conducted directly by CSL Behring and not by a market research company. The complaint arose following a transfer of value disclosure provided by CSL Behring in relation to the market research.

Sections of the Code
The conduct was alleged to be in breach of the following Sections of Edition 18 of the Code:

- Section 12.2 Market Research with Healthcare professionals

Response
In its response to the complaint, CSL Behring denied that its conduct of market research was in breach of Section 12.2 of the Code. CSL Behring stated that it had been clear to the participant that the activity was market research, that the market research was being conducted on behalf of a pharmaceutical company, and that the complainant had understood and accepted the presence of CSL Behring staff during the market research interview.

CSL Behring further responded that the complainant had signed a consent form prior to the market research interview, including in relation to the transfer of value reporting.

Code of Conduct Committee decision
The Committee found in a unanimous decision that there was no breach of Section 12.2 of the Code.

Sanction
Having found no breach of the Code, no sanction was considered.

Recommendations
Whilst no breach of the Code was found, the Committee recommended that CSL Behring consider:
1. Issuing a written apology to the complainant.
2. Including a clause in its market research agreement regarding the presence of a company representative at a market research interview.

Consideration of the complaint
The Chairman provided a brief summary of the complaint, as described above.

The Committee reviewed CSL Behring's response to the complaint and noted that the CNC had signed the consent to participate in the market research and, although they had questioned the presence of the CSL Behring employee at the market research interview, had agreed to proceed with the interview.

The Committee was concerned that it apparently had not been made clear to the CNC in advance that an employee of the company that had commissioned the market research would be present for the interview. The CNC would have expected to meet with a person from the market research company, as indicated in the CNC's emails provided by CSL Behring in its response to the complaint. On the other hand, it was also evident from the email exchanges that the CNC had agreed to proceed with the market research interview after becoming aware that the interview would be conducted with a CSL Behring employee present.

The Committee considered that it was unusual for a company representative to be present whilst a market research interview was being conducted. If this were to be the case, it would be expected that it would be explained to the participant in advance of the interview rather than the company person attending unannounced.

The Committee considered that whilst there appeared to have been no breach of Section 12.2 of the Code, because the CNC had consented to participate in the interview, there was also some misrepresentation to the CNC of the market research interview because the CNC had not been informed that a CSL Behring representative would be present. The CNC had felt they had been deceived, in spite of then continuing with the market research interview.

The Committee found in a unanimous decision that there had been no breach of Section 12.2 of the Code.
Whilst no breach of the Code was found, the Committee recommended that CSL Behring consider:
1. Issuing a written apology to the complainant.
2. Including a clause in its market research agreement regarding the presence of a company representative at a market research interview.

The Committee recommended that Medicines Australia consider including further clarification of this conduct in the Code of Conduct Guidelines.

1152 Keytruda Promotional materials

Subject Company: Merck Sharp & Dohme Australia Pty Ltd (MSD Australia)

Complainant: Novartis Pharmaceuticals Australia Pty Limited (Novartis)

Product: Keytruda (pembrolizumab)

Complaint

Novartis had alleged that promotional materials for Keytruda are in breach of the Code of Conduct because they contain promotional claims and visual representations based on data at a dose of Keytruda that is not included in the approved Product Information (PI).

Novartis alleged that the materials are misleading by implication of superiority at an unapproved dose, which risks the inappropriate use and off-label dosing of Keytruda for advanced melanoma.

Novartis referred to comparative superiority claims and visual representation based on the Keynote-006 study, which Novartis alleged evaluated doses of Keytruda not approved by the TGA and which are misleading by implication.

Sections of the Code

The promotional claims and materials were alleged to be in breach of the following Sections of Edition 18 of the Code:

- Section 1.1 Responsibility
- Section 1.3 False or Misleading Claims

Response

MSD Australia denied that its Keytruda promotional materials are in breach of the Code of Conduct. MSD Australia argued that the TGA and other regulatory agencies (US and EU) have approved the dose of 200mg of Keytruda every three weeks in advanced melanoma.

In its response to the complaint, MSD Australia stated that the dosing of Keytruda had evolved as evidence of the use of Keytruda for different indications has been published. MSD Australia stated that on 5 December 2018 the TGA approved a fixed dose of 200mg of Keytruda every 3 weeks for all indications. It noted that this differs from the dosage recommendation of 2mg/kg or 200mg every 3 weeks when the complaint was initiated by Novartis.

MSD Australia argued that its use of the Keynote-006 study data does not conflict with the PI and is consistent with it. MSD Australia stated that when referring to the Keynote-006 data in the materials, it had clarified any difference between a dose that was not currently recommended and the recommended dose in the PI.

Further to responding to the complaint, MSD Australia had alleged that Novartis has attempted to use the Code in a vexatious manner and that the complaint was without merit. MSD Australia had alleged that Novartis was in breach of Section 27 Abuse of the Code.

Code of Conduct Committee decisions

The Code of Conduct Committee made the following decisions in relation to the claims in the promotional materials:

Complaint 1: "Give your patients a key to superior overall survival (OS)"

The Committee found by majority decisions that the claim was not in breach of Sections 1.1 or 1.3 of the Code.

Complaint 2: Visual representations and promotional use of Keynote-006 study

The Committee found by majority decisions that the use of the Keynote-006 study in the promotional materials was not in breach of Sections 1.1 or 1.3 of the Code.

Allegation by MSD Australia of breach by Novartis of Section 27 Abuse of the Code

The Committee formed a unanimous view that the complaint did not contravene Section 27 of the Code. The complaint was not frivolous and Novartis should not be required to respond to the allegation.

Sanctions
Having found no breach of the Code, no sanctions were imposed.

Consideration of the complaint
The Committee noted that the complaint related to promotional materials for Keytruda, which included leave behind case studies presented by an oncologist and trade display panels. Novartis had alleged that the materials are in breach of the Code because they include reference to drug dosages for Keytruda that are not the same as the approved dose in the PI and that the materials claim superiority of Keytruda over ipilimumab.

The Committee noted that the Keytruda PI includes information from the Keynote-006 trial, in which patients were administered Keytruda at 10mg/kg every 2 weeks, every 3 weeks or ipilimumab. This information is in the Clinical Trials section of the PI. At the time the materials subject to complaint were published, Keytruda was approved for use at a dose of 2mg/kg or 200mg given every 3 weeks.

The Committee also noted that the approved dose of Keytruda was stated in the promotional materials wherever there was reference to the Keynote-001, Keynote-002 or Keynote-006 studies and the higher (10mg/kg) dose used in these studies. The Committee further noted that in the two case studies presented as leave behinds, it was stated that the patient received 2mg/kg every 3 weeks, the approved dose.

In its response, MSD Australia advised that in December 2018 the TGA had approved a change to the dose of Keytruda to a standard (adult) dose of 200mg every 3 weeks for all approved indications, which is consistent with changes approved by the US FDA and EU EMA.

The Committee referred to the Keytruda PI and MSD Australia's response to the complaint. It noted that the registration trials included in the PI showed there was similar efficacy and safety for pembrolizumab at 10mg/kg every 3 weeks and 2mg/kg every 3 weeks (Keytruda-002 trial). Whilst it is unusual for the Product Information to include doses that are not finally approved, the information from the Keynote studies is included in the PI and available to prescribers to review. The Committee noted that it is not unusual for the TGA to approved streamlined dosing regimens rather than different doses for different indications. There can be a lag between clinical information becoming available and the PI being updated to include this information.

The Committee discussed the superiority claim for pembrolizumab (Keytruda) versus ipilimumab in metastatic melanoma described in the promotional materials. The Committee noted that the claim was referenced to the Keynote-006 trial and the Keytruda PI. As already noted, data presented in the PI in the Clinical Trials section supports that there is similar efficacy and safety between the dose of pembrolizumab used in the Keynote-006 study and the approved dose. The Committee also referred to the pharmacokinetic data provided in the PI, which showed that there were no clinically meaningful differences in the pharmacokinetics of pembrolizumab across indications and dose ranges. Therefore, the Committee accepted that there was evidence to support the superiority claim as it had been presented in the promotional materials. The approved, recommended dose of Keytruda had been clearly visible in the materials wherever the Keynote-006 information appeared.

A minority of the Committee considered that it would not be sufficiently clear to a HCP that the Keynote-006 study compared a higher dose of Keytruda, 10mg/kg every 2 or every 3 weeks versus ipilimumab, which differs from the recommended and approved dose of 2mg/kg every 3 weeks. A minority of the Committee considered in the absence of formal demonstration of bioequivalence, between the 10mg/kg dose and the approved dose, or clinical equivalence of these doses in metastatic melanoma, superiority could not be claimed.

The Committee determined by majority decisions that the claim "Give your patients a key to superior overall survival (OS)" was not

in breach of Sections 1.1 or 1.3 of the Code of Conduct.

The Committee considered the overall use of the Keynote-006 use in the promotional materials, including in graphical representations of the data (complaint 2). A majority of the Committee considered that the use of the study in promotional materials was acceptable. The Keynote-006 study (and other Keynote studies) are included in the Keytruda PI and the doses used in this study have been shown to have the same efficacy and safety as the approved dose. The presentation of the study in the materials was not considered misleading by a majority of the Committee, because there was clear and frequent reference to the approved dose of Keytruda. A majority of the Committee did not agree that the materials encourage use of Keytruda at an unapproved dose. A minority of the Committee considered that in some materials, identified by Novartis in complaint 2, it was less clear that the Keynote-006 study used a higher mg/kg dose, which is not the approved dose.

The Committee determined by majority decisions that the visual representation and promotional use of the Keynote-006 study was not in breach of Sections 1.1 or 1.3 of the Code of Conduct.

The Committee discussed the allegation by MSD Australia that the complaint from Novartis was vexatious. Members considered that the dosage regimen used across the different studies reported in the PI was complex. The presentation of the data in the promotional materials had required considerable discussion within the Committee before reaching its decision. The Committee formed a unanimous view that the complaint was not vexatious and Novartis should not be required to respond to the allegation of a breach of Section 27 of the Code.

Sanctions
Having found no breach of the Code, no sanctions were imposed.