Medicines Australia Code of Conduct Quarterly Report January – March 2016

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 January and March 2016. Complaints finalised during this period were in relation to materials or activities conducted under Edition 18 of the Code.

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) are available from Medicines Australia. An order form is available from https://medicinesaustralia.com.au/code-of-conduct/code-of-conduct-current-edition/

The Code of Conduct 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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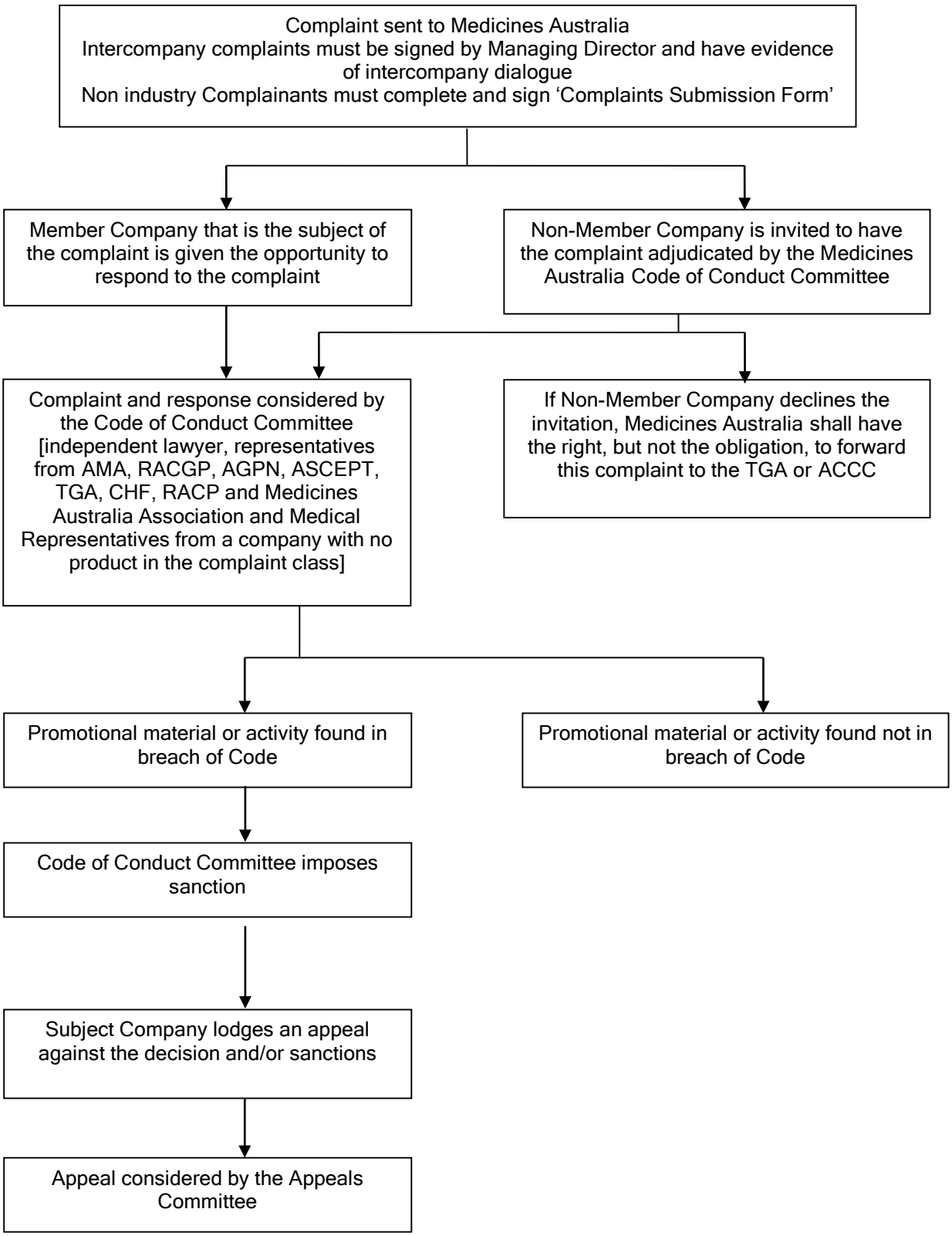
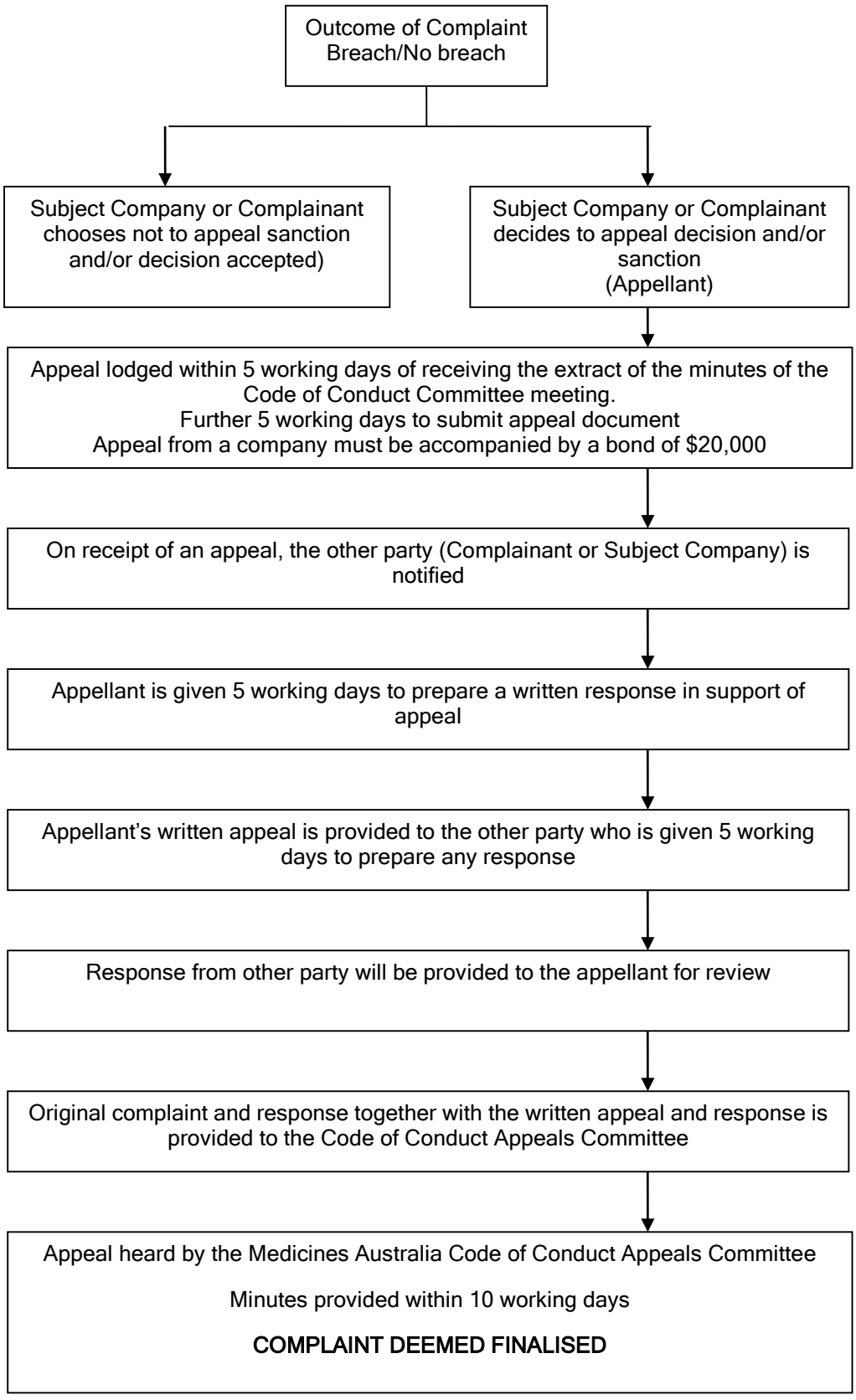
Medicines Australia Code of Conduct Complaints Handling Process



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 5 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 5 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 17 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 January – March 2016

No.	Subject Company	Material or Activity	Product	Complainant	Outcomes	Sanction
1134	Janssen-Cilag Pty Ltd	Promotional Claims	Zytiga	Astellas Pharma Australia Pty	Breach of Sections 1.2.2 and 1.3	Pay a fine of $100,000
1135	Bristol-Myers Squibb Australia Pty Ltd	Promotional Activities	Sprycel	Novartis Australia Pty Ltd	Breach of Section 1.3	Pay a fine of $50,000

1134 – Zytiga Promotional Claims

Subject Company: Janssen-Cilag Pty Ltd

Complainant: Astellas Pharma Australia Pty Ltd

Product: Zytiga

Complaint
Astellas alleged that Janssen had used the claims "MORE energy" and "MORE to live for" in its promotional campaign for its product Zytiga, which are not adequately supported by the findings of the referenced study. Astellas further alleged that the claims relating to fatigue management and energy promote Zytiga outside of its approved indication.

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

- 1.2.2 Level of Substantiating Data
- 1.3 False or Misleading Claims
- 1.4 Unapproved Products and Indications
- 1.6 Unqualified Superlatives

Response
Janssen rejected the allegations by Astellas and responded that the promotional material for Zytiga complied with the Code. Specifically, Janssen contended that the intended audience for the advertisements containing the claims, the specialised audience of medical oncologists, urologists and radiation oncologists with interests in uro-oncology, would have the background, context and experience to assess the claims. Janssen asserted that the campaign using the claims had not been distributed to a general practitioner audience.

Janssen further asserted that the claims in question were adequately qualified and were supported by sufficient evidence. Regarding the alleged off-label promotion of the potential energy gain, Janssen rejected Astellas' claims and asserted that there was no clinical outcome conveyed by the claim and its accompanying qualifier.

Code of Conduct Committee decisions
Issue 1: The Claim "MORE energy"
The Committee agreed in unanimous decisions that the claim "MORE energy" was in breach of Sections 1.2.2 'Level of Substantiating Data' and Section 1.3 'False or Misleading Claims' of Edition 18 of the Code of Conduct.

The Committee agreed in a unanimous decision that the claim "MORE energy" was not in breach of Section 1.4 'Unapproved Products and Indications' of Edition 18 of the Code of Conduct.

Issue 2: Placement of survival data together with "energy" data
The Committee agreed in a unanimous decision that the placement of the survival and "energy" data together was not in breach of Section 1.3 'False or Misleading Claims' of Edition 18 of the Code of Conduct.

Issue 3: The claim "ZYTIGA. MORE to live for"
The Committee agreed in a unanimous decision that the claim "ZYTIGA. MORE to live for" was in breach of Section 1.3 'False or Misleading Claims' of Edition 18 of the Code of Conduct.

The Committee agreed in a majority decision that the claim "ZYTIGA. MORE to live for" was not in breach of Section 1.6 'Unqualified Superlatives' of Edition 18 of the Code of Conduct.

Sanction
The Committee determined that the breaches of the Code were moderate as defined in the Code.

The claims found in breach of the Code must not be used again in the same or similar form; all promotional materials and/or advertisements containing the claims found in breach must be withdrawn from use and not used again in the same or similar form.

The Code of Conduct Committee also determined that Janssen-Cilag must send a corrective letter to all Australian medical oncologists, urologists and radiation oncologists with an interest in uro-oncology and to all attendees/registrants at the ANZ Urogenital and Prostate Annual Scientific Meeting (July 2015) and the Prostate Cancer World Congress held in Cairns in August 2015.

In addition, in a unanimous decision, the Committee imposed a fine of $100,000.

Appeal
Janssen appealed the decisions of the Code in relation to issues 1 and 3, arguing that the Committee had applied an incorrect test and had not analysed the materials from the

perspective of the applicable target audience. Janssen asserted that the materials were directed at a specialist audience who would be unlikely to be misled by the claims. Janssen also alleged that the Code Committee had erred in its decision making by not including a specialist clinician so that the Committee would have properly understand the context of the claims.

Janssen also appealed against the sanction imposed by the Committee, arguing that the Committee had not taken into account the extent of dispute resolution during the intercompany dialogue or the cost of undertaking corrective action.

Appeal Response
Astellas responded to the appeal, stating that the decisions of the Code Committee did not involve any error. Astellas reiterated its initial arguments supporting its complaint, that cancer-related fatigue is made up of a number of factors and that it is incorrect to assume that improvements in fatigue-related outcomes will be accompanied by an increase in energy levels.

Astellas noted that the Code of Conduct does not require that a specialist clinician participate in the consideration of a complaint. Further, Astellas asserted that it does not require a specialist clinician to determine whether or not a claim is supported by referenced data.

Astellas reiterated that it does not question the importance of cancer-related fatigue or quality of life outcomes, the validity of the tools used to measure such outcomes, nor the prestige of the journals in which the referenced studies were published. Rather, Astellas had alleged that Janssen's use of the claims "MORE energy" and "MORE to live for" do not adequately reflect the findings of the referenced studies and were misleading.

Appeals Committee decision
The Appeals Committee was not persuaded that the Code of Conduct Committee had erred in its decisions on any of the grounds that were raised in the appeal and agreed by majority decision to not uphold the appeal.

Sanction
The Appeals Committee agreed by majority decision that the fine of $100,000 imposed by the Code of Conduct Committee should not be varied. The corrective action required by the Code Committee was also confirmed by the Appeals Committee.

As the appeal had not been upheld in any aspect, the Appeals Committee agreed unanimously that the $20,000 appeal bond should be retained by Medicines Australia.

Consideration of the complaint
The Code Committee noted that the complaint related to three issues concerning a promotional brochure used in Janssen's "More" campaign for its product Zytiga, which was provided to medical oncologists, urologists and radiation oncologists with an interest in uro-oncology. The promotional material containing the claims subject to complaint was provided directly to these specialists by company sales representatives and was made available at specialist oncology conferences.

Issue 1: The claim: "MORE energy"
The Code Committee noted that the claim "MORE energy" was qualified by the following statement: *"Accelerated improvement in patient-reported fatigue intensity vs placebo in post-chemotherapy setting (ITT Population with clinically significant baseline fatigue); each in combination with prednisone".* Both the claim and qualifying statement are referenced to a study by Sternberg et al (Sternberg CN, et al. Ann Oncol 2013; 24:1017-1025) (the Sternberg study).

The Code Committee discussed the association between "fatigue intensity" and "energy". The Committee did not agree with Janssen's assertion that a reduction in fatigue would give a patient more energy. The Committee considered that the claim "MORE energy" relied on there being an association between fatigue intensity and energy, but there is not sufficient evidence to support that association. The Committee did not agree that the Sternberg et al study provided evidence to support that an improvement in fatigue intensity is equivalent to having "more energy". Fatigue intensity is not a surrogate indicator for energy – fatigue and energy are different things. Further, the Code Committee noted that the Approved Product Information for Zytiga did not make any reference to the reduction of fatigue or greater energy.

The Code Committee considered that Janssen had made a simplistic interpretation of a reduction in fatigue intensity being equivalent to having "more energy" which could not be adequately supported by the referenced study.

The Code Committee agreed in a unanimous decision that the claim "more energy" was in breach of Sections 1.2.2 and 1.3 of the Code

of Conduct because it could not be adequately supported by the cited evidence and was therefore misleading.

The Code Committee discussed the allegation that this claim may lead healthcare professionals to prescribe the product to treat fatigue, which is not an approved indication for Zytiga. The Code Committee agreed that in consideration of the audience for the promotional material, which was provided to specialists in the treatment of prostate cancer, it would be unlikely that the product would be prescribed for the treatment of fatigue. The Code Committee unanimously determined that the claim "more energy" was not in breach of Section 1.4 of the Code of Conduct.

Issue 2: Placement of survival data together with "energy" data

The Code Committee noted that this issue in the complaint related to placing the "energy" claim and a graph depicting the time to improvement in fatigue in patients treated with Zytiga and prednisone on the same page as the statement *"41% increase median overall survival"*. The Committee considered that a healthcare professional reader would be able to easily discern that these two claims were separate statements and would not conflate them or interpret them to mean that "more energy" was associated with improved survival. The two claims are clearly referenced to two different studies. The Committee determined in a unanimous decision that there was no breach of Section 1.6 of the Code of Conduct.

Issue 3: The claim "ZYTIGA. MORE to live for"

This part of the complaint related to the claim "MORE to live for" and the qualifying statement "*increased median overall survival vs placebo with maintained quality of life; each in combination with prednisone*". The qualifying statement was referenced to the Approved Product Information and four published studies.

The Committee considered that an improvement in fatigue symptoms and increased median overall survival may not necessarily give a patient "more to live for". The Code Committee thought that it was overreaching beyond the evidence in the Product Information or the four referenced studies to make this claim. The Committee were of the opinion that the referenced studies do not support a change in the patient's state of mind such that they would feel they have "more to live for". Further, the claim "MORE to live for" is a heading for the other claims on the same page relating to "more survival", "more time without chemotherapy" and "more energy", which do not necessarily lead to a patient feeling they have "more to live for". The Code Committee determined in a unanimous decision that the claim *"MORE to live for"* was false and misleading and in breach of Section 1.3 of the Code.

The Code Committee discussed whether the claim was also in breach of Section 1.6. A minority of the Code Committee members considered that the claim was an unqualified superlative, which implied a unique property of the product such that it could improve a patient's outlook on life. The majority of the Code Committee members, however, considered that the claim was not implying or asserting that Zytiga was unique or had some special merit or general superiority. Therefore, the Committee agreed by a majority decision that the claim was not in breach of Section 1.6 of the Code of Conduct.

Sanction

Having found breaches of the Code of Conduct, the Code Committee discussed the severity of these breaches. The Code Committee agreed by unanimous decision that the breaches were moderate as defined in the Code of Conduct.

The Code Committee agreed by unanimous decision that:

- The claims found in breach of the Code must not be used again in the same or similar form;
- All promotional materials and/or advertisements containing the claims found in breach must be withdrawn from use and not used again in the same or similar form.
- Janssen-Cilag must send a corrective letter to all Australian medical oncologists, urologists and radiation oncologists with an interest in uro-oncology and to all attendees/registrants at the ANZ Urogenital and Prostate Annual Scientific Meeting (July 2015) and the Prostate Cancer World Congress held in Cairns in August 2015.
- Janssen-Cilag must pay a fine of $100,000.

Consideration of the Appeal

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 the Janssen representatives to give their appeal presentation to the Appeals Committee. The following summarises that presentation and discussion with the Appeals Committee.

Janssen noted that the brochure for Zytiga was found in breach in relation to two aspects. Janssen wished to focus on the central and practical question as to whether these two aspects were misleading to the oncologists who received it, explain how the target audience would read the material, and to explain why Janssen thought the brochure appropriately promotes the virtues of the medicine.

Janssen emphasised that the underlying purpose of the Code is to ensure the Quality Use of Medicines (QUM) with the health of patients being the primary objective. It was Janssen's view that the messages conveyed in the brochure were simple and direct.

Claim: "*More Energy*"

Janssen contended that the Code Committee had erred in its decision to find the claim *"More Energy"* to be misleading because it did not take into account the qualifications, competencies and experience of the target audience. Rather, Janssen contended, the Code Committee considered the claim from the point of view of a lay person or a general practitioner, whereas the brochure would not be read by them. Janssen noted that the brochure was intended to be read by specialist oncologists who treat advanced stage prostate cancer patients. It was Janssen's contention that the claim and the supporting reference would be correctly understood by that audience.

Janssen invited the Appeals Committee to have regard to the whole of the brochure, rather than just the claims subject to complaint. Janssen argued that marketing materials typically include a headline – a statement to attract attention – and this item is no different. However the qualifying statement directly below the headline claim explains and provides the proper interpretation of the claim. Janssen argued that the claim must be considered in its entirety with the qualifying statement, rather than the headline alone.

Janssen emphasised the nature of the product being promoted in this brochure, noting that it is not a sports drink or similar item sold on supermarket shelves – with catch cries that it produces energy. Janssen asserted that this is a serious drug has been shown to increase overall median survival and improve reported fatigue intensity in patients. Janssen argued that it is important that the Appeals Committee does not prevent the promotion of this product unless the Committee is really satisfied that the claim is misleading. Janssen appealed to the Appeals Committee to not get caught up in marketing techniques and "linguistic gymnastics", but to focus on what an oncologist would understand from reading the brochure and would it mislead them.

Janssen then discussed fatigue as it relates to prostate cancer treatment. Janssen advised the Appeals Committee that fatigue is a recognised recordable adverse event in patients receiving treatment for this type of cancer. In a clinical setting, however, fatigue is described in a variety of ways: tiredness and lacking in energy are examples of words regularly used by patients.

Janssen urged the Appeals Committee to consider the statement *"More energy"* and ask whether the oncologist seeing these words would immediately prescribe Zytiga in patients that are experiencing fatigue during their treatment. Janssen's contended that this is very unlikely. Janssen considered that the specialist audience would continue reading the brochure, particularly the qualifying statement *"Accelerated improvement in patient-reported fatigue intensity vs placebo in post-chemotherapy setting (ITT population with clinically significant baseline fatigue) each in combination with prednisone."*. It is this qualifier in association with the claim *"More energy"* that Janssen considers is the key message in the brochure. Janssen contended that the claim *"More energy"* is in relation to the patient's expected response to the treatment being advertised. Taken together, the claim and the qualifier explain that a patient is likely to achieve an improvement in their level of fatigue intensity. Janssen also noted that an improvement in fatigue intensity often causes patients to say they have 'more energy'.

Janssen contended that the claim *"More energy"* and the qualifying statement are adequately supported by the Sternberg et al (2013) study. Further, Janssen contended that the claim *"More energy"* is not about how the result is achieved physiologically; the claim isn't about the composition of Zytiga and whether it contains a specific ingredient that creates energy. It concerns what patients feel

and they reported feeling less fatigued during treatment.

Janssen commended the statement supplied from a specialist oncologist dated 22 December 2015 (Dr Siobhan Ng) to the Appeals Committee. This statement supports Janssen's arguments for how a specialist oncologist audience would read the brochure and the claims in question. The specialist oncologist stated in her letter that *"the term 'fatigue' is a recognised, recordable adverse event in any clinical trial. It is the only term to describe this feeling that is on the National Cancer Institute Clinical Toxicology Criteria (NCI-CTC) list of adverse events… Patients may express themselves variously as having 'tiredness', 'lacking in energy', 'useless', 'weak' and sometimes 'fatigued'. The clinician then asks questions to determine if the symptom the patient is describing fits into the NCI-CTC criteria definition of fatigue."* Janssen asked the Appeals Committee to note that in their submission, the specialist oncologist had declared that they are a participant in advisory boards for both Janssen and Astellas, as well as being an investigator in clinical trials involving prostate cancer treatments for both companies. Janssen therefore rejected Astellas' allegation, in its response to the appeal, that the specialist oncologist was biased in favour of Janssen.

An Appeals Committee member sought clarification on fatigue as a recognised adverse event in the NCI-CTC, noting that the rating scale used in the NCI-CTC is different to that used in the Sternberg et al (2013) study. Further, the Appeals Committee member noted that the baseline rates of fatigue were high in the Sternberg et al (2013) study, but there appeared to be tension between the reporting of reduced fatigue and emergent fatigue. Janssen responded noting that it is important to go back to the way fatigue was mentioned, and noted that the NCI-CTC is brief in its definition. Janssen noted that the Brief Fatigue Inventory (BFI) instrument had been used because there wasn't a great deal of a difference in the reported incidence of fatigue between the arms of the study. Importantly, Janssen noted that this assessment had been identified in the exploratory analysis for the study and had been implemented as part of the original study design – it was not a retrospective analysis. Janssen also noted that Sternberg et al (2013) had found a difference in fatigue intensity between abiraterone (Zytiga) and placebo which showed that patients taking the study drug had improved fatigue intensity.

Janssen asserted to the Appeals Committee that the claim *"More energy"* relates simply to the patient reported feeling of fatigue, and that it is qualified appropriately and well supported by the Sternberg et al (2013) study. Janssen reiterated that the claim does not imply that Zytiga creates energy and believed it would be surprising for a clinical oncologist in this area would be misled by the statement.

Claim: "*More to live for*"

Janssen reiterated its view that the Code Committee had erred in its decision making process in relation to the claim *"More to live for"*. Janssen's argued that the intended audience would take the statement on its face value and would apply their knowledge and expertise to its interpretation. Further, Janssen contended that when read in conjunction with the qualifying statement appearing immediately below the claim, *"Increased median overall survival vs placebo with maintained quality of life; each in combination with prednisone"*, a specialist oncologist would have the knowledge to understand that statement. Janssen submitted that the Code Committee's error was revealed in its reasons for decision which denoted that *"The [Code] Committee considered that an improvement in fatigue symptoms and increased median overall survival may not necessarily give a patient 'more to live for'".* Janssen believed that the Code Committee's interpretation was giving a meaning to the words that went beyond the meaning explained in the brochure. Janssen was not representing to oncologists that it guaranteed that the patient had generally more to live for. By common sense the claim is limited by the realities of the drug itself.

Janssen emphasised that the statement was substantiated adequately by the Sternberg et al (2013) and Harland et al (2013) studies. These studies demonstrated that treatment with medication provided an improvement in patient quality of life, and that Zytiga is a drug that delivers real and meaningful benefits to patients. Janssen considers that the matters of quality of life and survival are sensibly summarised by the notion of "*More to live for*" and that notion is explained in the brochure itself. The quality of life of patients who are at this stage of cancer is deteriorating over the course of treatment, and Zytiga counters this deterioration and helps maintain the quality of life that would ordinarily be reduced. Further,

Janssen asserted that the comparison made is between Zytiga and placebo, and not to any competitor product.

Sanctions

Janssen concluded its presentation stating that it hoped that the Appeals Committee would find Janssen's observations and arguments persuasive and find that neither aspect of the brochure is misleading. Janssen asked the Appeals Committee to take into account the views expressed and be satisfied that Janssen had not deliberately or recklessly acted to mislead and that it holds firm the genuine belief that the behaviour is appropriate. Janssen asked the Appeals Committee to review the size of the fine imposed by the Code Committee, requesting that should the appeal not be upheld, that the size of the fine be reduced.

At the conclusion of Janssen's presentation, the Appeals Committee sought some clarifications.

The Appeals Committee sought further explanation of how the 'energy' terms are used in the referenced studies and their understanding by the target audience. Janssen responded that the terms 'fatigue', 'lack of energy', 'tired' and other energy synonyms are used interchangeably by patients in this community and by healthcare professionals treating these patients. Specialist oncologists don't see the word in isolation, but in context of the patient's treatment. It was further clarified that the statement is to be taken to mean that Zytiga doesn't give patient's energy, but that it reduces fatigue and that the reduction in fatigue is often described by patients as 'more energy'.

The Appeals Committee Chairman requested clarification of Janssen's concerns relating to the lack of a clinical oncologist on the Code Committee. The Chairman noted that the membership of the Code Committee is set out in the Code of Conduct, which does not include a clinical specialist for matters to be heard. The inclusion of a specialist is a requirement for an Appeals Committee only. Janssen responded that it was not challenging the composition of the Code Committee but there not being a specialist oncologist on the Code Committee made it more difficult for the Committee to interpret the brochure from the perspective of its intended audience.

An Appeals Committee member queried the reach of the distribution of the brochure and the claims subject to complaint. Janssen responded that the brochure had been developed for interactions with a small specialised audience in a limited print run. The brochures were used at congresses with a largely specialist oncologist audience. Janssen relied on the advice of the ANZUP congress organisers in relation to the make-up of the delegates, but accepted that there would have been registrars, doctors in training, other interns and non-specialised healthcare professionals in attendance.

The Chairman then invited Astellas to make its presentation in response to the appeal.

Astellas thanked the Appeals Committee for the opportunity to reinforce its complaint and reiterate the ongoing concerns first raised with Janssen in July 2015. Astellas commenced its presentation by referring to the medical definition of 'energy', citing the following definitions:

- McGraw-Hill Concise Dictionary of Modern Medicine
  - *"The capacity to do work, measured in joules. Types Potential/stored energy, kinetic/in motion energy."*
- Mosby's Medical Dictionary
  - *"The capacity to do work or to perform vigorous activity. Energy may occur in the form of heat, light, movement, sound, or radiation. Human energy is usually expressed as muscle contractions and heat production, made possible by the metabolism of food that originally acquired the energy from sunlight. Chemical energy is that released as a result of a chemical reaction, as in the metabolism of food*."
- Dictionary of Sport and Exercise Science and Medicine by Churchill Livingstone
  - *"The capacity to do work. Includes kinetic, gravitational, potential, elastic potential, heat, sound, chemical, nuclear.*
    Measured in joules or calories."

Astellas contended that these definitions are very consistent, and urged the Appeals Committee to keep in mind that a healthcare professional audience would take *"more energy"* to be understood in that context. Astellas also asserted that it agreed that the qualifying statement was acceptable and had been referenced to a reputable journal. It is Astellas' complaint, however, that there is a

disconnection between the headline claim "More energy" and the qualifier.

Astellas noted that the Sternberg et al (2013) study used the Brief Fatigue Intensity Questionnaire (BFIQ), in which the outcome is based on a single question around a subjective patient response at baseline and at time points thereafter. Astellas emphasised that it was not challenging the validity of the BFIQ. However, in the context of the fatigue intensity improvement assessment, a change in capacity to do work was not measured, nor was a change in joules/calories. Therefore Astellas' asserted that a change in "energy" was not measured by Sternberg et al (2013).

Astellas recapped its original complaint for the Appeals Committee:

- An accelerated improvement in fatigue intensity is not sufficient evidence to support the "more energy" claim.
- Patient reported outcomes (BFI) were insufficient to support "more energy" as changes in energy were not measured.
- Cancer related fatigue has a complex aetiology
- "More Energy" is an inaccurate extrapolation of fatigue intensity; is not unequivocal; is not supported by the literature; and is misleading.
- Astellas continues to believe this claim breaches Sections 1.2.2 and 1.3 of the Code

Astellas discussed Janssen's reference in its appeal to a case heard by the Federal Court between Novartis Pharmaceuticals and Bayer Australia. Astellas argued that this case, which related to the understanding of a dominant message by a target audience, was not relevant to Astellas' complaint against Janssen, which concerned the use of appropriately substantiated claims as related to the referenced data. Nevertheless, Justice Robertson had ruled that regardless of the specialised nature of the intended audience, they are not immune to advertising.

Astellas then discussed Cancer Related Fatigue (CRF) which is one of the most common problems experienced by cancer patients. CRF is defined as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and that interferes with usual functioning. It is widely accepted that the aetiology of CRF is complex and has a variable pattern of clinical expression driven by a multi-dimensional interaction of somatic, emotional, cognitive, and psychosocial factors.

Astellas referred to an article by Dimeo, F. C. (2001), which had been provided by Janssen in its response to the original complaint. This article stated that patients may describe fatigue in different ways, including mental fatigue, volitional fatigue and physical fatigue. The Dimeo article stated that whilst a subjective feeling of tiredness, weakness or lack of energy might be used to describe fatigue, physiologically (as opposed to perception) there are many factors such as depression, anxiety, sleep disruption, among others that contribute to fatigue. Astellas asserted that it is fundamentally incorrect to extrapolate that an improvement in fatigue intensity is a result of "*More energy*" provided by Zytiga.

Astellas further noted that the Sternberg et al (2013) commentary conflicts with the claim of "*More energy*" as at no stage do the authors state that the observed improvements in fatigue are in any way related to "energy". Astellas contended that the Sternberg et al (2013) study found that *"The benefits of abiraterone acetate to patient-reported fatigue could be the result of amelioration in tumour burden and/or disease progression. However, this hypothesis requires additional study…"*. Astellas contends that the fatigue outcomes were not well correlated and showed insufficient evidence to be conclusive. Further, the Sternberg et al (2013) study noted that *"…we did not attempt to determine the mechanism underlying fatigue improvement. Cancer-related fatigue, as a consequence of both the disease and its treatment, is a complex phenomenon influenced by numerous physiological factors."* Therefore, Astellas argued, Janssen had oversimplified a complex issue by using an inaccurate and misleading extrapolation. Finally, in its conclusion, Sternberg et al (2013) noted that *"it is not surprising that an agent shown to improve pain, and physical and emotional wellbeing also improves fatigue"*. Astellas contended that this highlights that fatigue intensity is not a surrogate for energy.

Astellas maintained its view that the claim "*More energy*" in association with Zytiga was neither appropriately substantiated, balanced, accurate, correct nor supported by the referenced study. Therefore, Astellas confirmed its position that the claim was in breach of Sections 1.2.2 and 1.3 of the Code.

In addressing the claim *"More to live for"*, Astellas reiterated that the claim was misleading and was not supported by the qualifying statement. Astellas asserted that patients' quality of life was maintained and not enhanced and that using a quality of life measure seeks to quantify the wellbeing of an individual's life. Astellas contended that Janssen could assert that an individual has a greater purpose or reason to live, such as the claim "*More to live for*". The converse of such a claim is that those patients who do not take Zytiga would have less to live for, which Astellas also considered to be incorrect. Astellas stated that the quality of life data is not in question in this case, but contend that there is a disconnection between the headline and the qualifying statement. Astellas argued that Section 1.2.2 of the Code requires that *"evidence to support any claim that will have a significant impact on the prescribing of a product must be unequivocal and the highest quality"* and contended that a subjective state of mind response does not meet that standard.

Astellas turned to the supporting evidence supplied by Janssen from specialist oncologists and expressed the view that Janssen would align only with healthcare professionals whose opinion reflects with their own. Therefore the opinions can only be viewed as being biased. Astellas rejected the interpretations put forward in these statements that a claim can mean something other than what is written. Further, Astellas pointed out that in one of the supporting letters, one healthcare professional had misinterpreted the statement *"more to live for"* as suggesting an improved quality of life rather than the maintenance of quality of life, as was stated in the qualifying statement. Astellas suggested that this was further evidence that the audience could be misled by the claims.

Astellas rejected Janssen's assertion that the brochure containing the claims was shown to a limited audience and detailed that it had been used in the following conferences and publications:

- Conferences/Congresses: ANZUP 2015, PCWC 2015, SIU 2015.
  - Satchel inserts / handouts
  - Trade display stand panels
- Publication – claims contained in an advertisement in:
  - *Prostate Cancer Research Review*, 2014
- Wide Audience:
  - Oncologists and urologists of varying degrees of clinical experience
  - Conference delegates (wide-range of allied HCPs)
  - All those with on-line access to *Research Review*

Astellas concluded that the Code Committee had not erred in its original decisions.

The Appeals Committee did not seek further clarification from Astellas on its presentation. The Chairman then invited Janssen to make its closing remarks.

Janssen responded that the fundamental defect in Astellas' position is the repeated reference to the disconnection between one part of the brochure and another. Janssen contended that to do so treats the qualifier as though it doesn't provide an explanation for the words that appear immediately above it. Rather than recognising the relationship between the words "*More energy*" on one hand and the words that follow it, Janssen asserted that Astellas seek to look outside the document and apply layman or other medical definitions to the terminology. The definition of *"More energy"* can be found immediately below the claim in the qualifying statement.

Astellas had referred to a previous Code of Conduct complaint in which the words "more energy" had been found in breach of the Code. Janssen responded that this case should be read in its entirety, which reveals that the claim was to the public at large and related to an entirely different product. Therefore this other complaint is of no assistance to the Appeals Committee.

Janssen addressed the criticisms of the specialist oncologist's statement, noting that the individual in question accepted that if the brochure was intended to be read by those outside the target audience, such as laypersons or those without context, it is liable to be misinterpreted by those individuals. Janssen asserted that this is not controversial; but it is irrelevant to the Appeals Committee in deliberating on this matter.

Finally, Janssen advised that the only people that can prescribe this product are specialist oncologists. These specialists have been the sole target for this promotional material in the context of conferences. However, Janssen cannot exclude the possibility that this claim has been visible to others through a variety of

mechanisms as pointed out by Astellas. It is Janssen's belief that this is inconsequential as those individuals are unable to prescribe the product, and were not the target audience for the promotional claims.

Janssen concluded its argument by reaffirming that the definition of the claims can be found in the document itself. The Appeals Committee should take into account the specialised context in which the brochure will be read and invited the Appeals Committee to bring that context to bear in its deliberations.

The Chairman thanked the representatives from Janssen and Astellas for their presentations and excused them from the meeting to allow the Appeals Committee to deliberate on the appeal.

The Appeals Committee discussed the audience for the Zytiga brochure that contained the claims subject to complaint, noting that while it is true that this product is typically prescribed by a specialist oncologist, there is also a small group of urologists who treat patients with advanced metastatic prostate cancer. The Appeals Committee accepted that whilst the audience at congresses such as the Australian and New Zealand Urogenital and Prostate (ANZUP) Cancer Trials Group Annual Scientific Meeting, where the brochure was used, is intended to be specialists, there is often attendance by others such as medical students, registrars, general practitioners and nurses. Whilst Janssen's intended audience for the brochure was the specialist oncologists and urologists who may prescribe Zytiga, it is difficult in today's environment to restrict advertising to a single audience.

The Appeals Committee discussed the proper use of a headline claim and qualifying statement associated with that claim. The Appeals Committee agreed that it is legitimate to use a headline to grab the reader's attention and to convey further explanatory information from a report or study on the same page such as in a qualifying statement. The underlying question in this case is how the specialist audience would read and interpret the headline claim.
The Appeals Committee considered that it would not be consistent with the Code to select particular words as a headline claim that may not specifically reflect the supporting reference, and then seek to limit or explain the claim's meaning through a qualifier. The Appeals Committee agreed that the central issue is whether the headline claim "*More energy*" misrepresents what follows in the qualifier and the supporting references.

The Appeals Committee considered that Astellas' reference to medical dictionary definitions for energy as relating to joules/calories was spurious and dismissed this argument.

The Appeals Committee acknowledged that a clinician may speak with patients in layperson terms. However, the Appeals Committee considered that because the audience for the brochure and the claims is a specialist one, and that fatigue is a complex syndrome in cancer treatment, the use of the claim "*More energy*" in promotion to that group is only acceptable if it can be supported by relevant evidence. The Appeals Committee noted that Janssen had emphasised the specialist audience in its appeal, drawing attention to their medical and technical expertise. Therefore the terms used in promotional materials should not be open to varying interpretations but should concisely and consistently reflect the supporting evidence. The Appeals Committee also considered that, as there are numerous components to cancer related fatigue, it is too simplistic to describe it as "*More energy*".

One Appeals Committee Member was of the opinion, however, that whilst agreeing that cancer related fatigue is complex, and that energy is also complex, the result of having less fatigue is more energy. This Appeals Committee Member was of the opinion that the use of the claim *"More energy"* captured the attention of the reader and had been appropriately qualified. This Appeals Committee member considered that the term 'more energy' is synonymous with 'less fatigue'. It was this member's opinion that the use of the global term 'energy' satisfactorily captured the overall patient reported outcome noted in the BFIQ. The Appeals Committee Member remained unconvinced that the claim could mean anything other than less fatigue equals more energy. This Appeals Committee Member agreed that the qualifier was necessary and without it the claim would be misleading.

The majority of the Appeals Committee disagreed that improved fatigue intensity, as demonstrated by the cited reference, equates to "*More energy*". Therefore the Appeals Committee agreed by majority decision with the Code Committee's decision that the claim

"*More energy*" was in breach of Section 1.2.2 of the Code of Conduct as it could not be adequately supported by the cited reference. The Appeals Committee also agreed by majority with the decision of the Code Committee that the claim was in breach of Section 1.3 of the Code of Conduct as it was misleading.

The Appeals Committee then discussed the claim *"More to live for"* and agreed that many of the arguments it had discussed in relation to the "energy" claim also applied to this claim. The Appeals Committee noted that the specialist oncologist's submission provided by Janssen showed that they were initially also misled by the claim, which the specialist had interpreted as relating to a wide therapeutic window and improving (not maintaining) quality of life. The Appeals Committee noted that the qualifying statement for "*More to live for*" stated that quality of life was maintained rather than improved. Therefore, the claim "*More to live for*" was not consistent with the qualifying statement or the supporting reference. However, one Appeals Committee Member contended that, similarly to the "energy" claim, the intended audience would understand that it was not an absolute statement of claim and, in the context of the treatment of patients with advanced prostate cancer, a longer life would not necessarily mean a better life. The Committee accepted that an oncologist may discuss with an individual patient the trade-off between quantity (duration) and quality of life.

The Appeals Committee in the majority agreed with the Code Committee's reasoning that improved survival and maintenance of quality of life, as supported by the cited references, does not mean that a patient will have more purpose or reason for living or "*More to live for*". The Appeals Committee agreed by majority with the decision of the Code Committee that the claim *"More to live for"* was misleading and in breach of Section 1.3 of the Code of Conduct.

Sanction
As the appeal was not upheld, the Appeals Committee considered whether there was any reason that the sanction should be varied. Although Janssen had asked the Appeals Committee to take into account the resolutions achieved during intercompany dialogue with Astellas, this is not a reason to reduce the fine as it is required by the Code of Conduct. The Committee noted that the maximum fine for a moderate breach of the Code is $150,000. The fine of $100,000 is therefore not at the upper end of the scale. The scope of the corrective action required was not such that the Appeals Committee considered there should be any reduction in the monetary fine. The Committee agreed by majority decision that it had not been persuaded there was any reason to vary the sanction and confirmed that the fine of $100,000 imposed by the Code Committee should remain. Further, as the appeal had not been upheld, the Appeals Committee agreed unanimously that the appeal bond of $20,000 should be retained by Medicines Australia.

1135 – Sprycel Promotional Activities

Subject Company: Bristol-Myers Squibb Australia Pty Ltd (BMSA)

Complainant: Novartis Australia Pty Ltd

Product: Sprycel

Complaint
Novartis alleged that in two promotional items, BMSA had focussed on efficacy and downplayed the safety aspects and overall management of patients experiencing pleural effusion while on Sprycel treatment.

Novartis alleged that claims concerning response rates to Sprycel in patients with pleural effusions did not adequately explain the complexity of dose reductions, treatment interruptions and interventions required to manage pleural effusions, which was misleading. In addition, a flow chart describing the management of patients with pleural effusions misrepresented the recommendations for managing this adverse event described in the Sprycel Product Information, which was therefore misleading. Further, Novartis alleged that BMSA had selectively presented data in a forest plot of adverse events by omitting an odds ratio for pleural effusion in Sprycel patients. Novartis contended that the omission of pleural effusion was misleading.

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

- 1.3 False or Misleading Claims

Response
BMSA denied that it had misrepresented information about pleural effusions in the promotional pieces and denied that the promotional material was in breach of the Code.

BMSA asserted that the management of pleural effusion had been adequately represented, noting that the promotional piece was designed specifically to discuss the treatment of pleural effusion. BMSA strongly rejected that the flow diagram oversimplified the management of pleural effusion, as it incorporated all the common and typical management strategies as stated in the Sprycel approved Product Information.

BMSA also denied that the forest plot was misleading because the incidence of pleural effusion had been clearly stated below the plot. BMSA further argued that the odds ratio for pleural effusions had not been calculated in the referenced article and that it would not be appropriate to calculate it post analysis and include it in the forest plot.

BMSA expressed concern to the Committee of the frequency, nature and timing of Novartis' complaints. Specifically, BMSA noted that this is the third consecutive year that a complaint had been made in the weeks leading up to the annual HAA meeting and alleged that Novartis had specifically timed the complaints to create maximum disruption. BMSA advised that the material containing the forest plot had not been in use since February 2015.

Code of Conduct Committee decision
- The claim "in first-line CP-CML, pleural effusions did not impair the ability of patients to achieve a response" was found by majority decision to be in breach of Section 1.3 of the Code.
- The flow chart describing management of patients who experienced pleural effusion was found by majority decision not to be in breach of Section 1.3 the Code.
- The forest plot detailing adverse events was found by unanimous decision to be in breach of Section 1.3 of the Code.

Sanction
The Committee agreed by majority decision that the promotional materials must be withdrawn from use and the content found in breach must not be used again in the same or similar form. The Committee also agreed by majority decision to impose a fine of $50,000.

Consideration of the complaint
The Committee noted that the complaint was difficult to navigate, as some issues had been resolved during intercompany dialogue whilst others had not. The complaint described two issues being subject to complaint, whereas one issue included two separate matters. The Committee determined that there were three matters that remained unresolved following intercompany dialogue:

1) Whether the claim *"In first line CP-CML, pleural effusions did not impair the ability of patients to achieve a response"* and associated data on response rates and pleural effusion by year of treatment were imbalanced and therefore misleading. This claim and data appeared in two promotional items SPR/0121/10-14 and SPR/0372/07-15;
2) Whether the flow chart *Managing pleural effusion,* which appeared in promotional item SPR/0121/10-14, was misleading; and
3) Whether the omission of a pleural effusion odds ratio from the forest plot titled *"Adverse events in ≥ 10% of patients at 5 years (no Grade 5)",* which appeared in promotional item SPR/0121/10-14, was misleading.

Issue 1: *"In first line CP-CML, pleural effusions did not impair the ability of patients to achieve a response"*
Novartis had alleged in its complaint that this claim and the associated data on different measures of response rates (confirmed complete cytogenetic response [cCCyR], major molecular response [MMR] and molecular response [MR]) was imbalanced and had the potential to mislead prescribers. Specifically, the complexity of dosing adjustments and interruptions required in patients with pleural effusions, although ultimately achieving these efficiency results, is omitted from the promotional pieces where the claim appeared. This dosage adjustment information is described in the supporting reference (Cortes J., et al 2014) and is supported by the Sprycel Product Information.

The Committee agreed with the complainant that the claim that pleural effusions "did not impair" achieving a response and the associated response rate information was misleading due to its emphasis on efficacy (response rates) and the omission of contextual information on the requirement in the study for Sprycel dosage adjustments. The words "did not impair" suggests that there was no relationship between pleural effusion

and achieving a response, whereas the response rates were only achieved following adjustments to Sprycel treatment. The Committee considered that claim emphasised response rates to Sprycel and downplayed the effects of the common, serious adverse effect of pleural effusion, which was not appropriate and was misleading. In a majority decision the Committee found the claim "*In first line CP-CML, pleural effusions did not impair the ability of patients to achieve a response*" was in breach of Section 1.3 of the Code of Conduct.

Issue 2: Flow diagram titled *"Managing pleural effusion"*
The Committee noted that this complaint had been raised during intercompany dialogue in relation to issue one. The Committee further noted that during intercompany dialogue BMSA had agreed to include additional information in "Consider additional measures" box of the flow chart.

A majority of the Committee considered that the flow chart sufficiently covered the management of pleural effusion. Whilst it was presented as a simple flow chart, the steps covered how pleural effusion is managed by physicians. The Committee noted that the flow chart was adapted from NCCN guidelines and was consistent with the Sprycel Product Information guidance on managing this adverse effect.

A minority of the Committee were of the opinion that the flow chart was inadequate and therefore was misleading. These Committee members considered that there are a significant number of people who experience a pleural effusion while on Sprycel treatment and a significant number of these require more than a dose reduction and treatment with diuretics and steroids. These Committee members considered that the flow chart was overly simplistic and minimised the seriousness of the adverse event and the interventions that may be required to treat it.

The Committee agreed by majority decision that the flow chart was not in breach of Section 1.3 of the Code of Conduct. Whilst not finding the flow chart in breach of the Code, the Committee encouraged BMSA to proceed to make the amendments agreed during intercompany dialogue.

Issue 3: Forest plot titled *"Adverse events in ≤ 10% of patients at 5 years (no Grade 5)*
The Committee considered the alleged breach because the forest plot did not include an odds ratio for the prevalence of the adverse event pleural effusion. An asterisked statement linked to the heading appeared in smaller type size below the forest plot: *"Pleural effusion (28%) is not shown to allow adequate representation of other events"*. The Committee noted that, below the forest plot, data on pleural effusion by year of treatment were provided, however that these data were separated from the forest plot. The Committee was of the opinion that by separating the information on pleural effusion from the forest plot the effect was to minimise or reduce focus on the higher prevalence of pleural effusion in patients treated with Sprycel compared with imatinib and maximise attention on adverse effects where the odds ratios favoured Sprycel over imatinib. The Committee considered that this would make it more difficult for a prescriber to evaluate the overall adverse event profile for Sprycel. The Committee were concerned that the presentation of the data on pleural effusion and omission of the odds ratio for pleural effusion from the forest plot would have the effect of downplaying the higher prevalence of pleural effusion in patients treated with Sprycel compared with those treated with imatinib.

The Committee discussed BMSA's argument that the odds ratio had been omitted from the referenced source for the forest plot and that the company should not calculate the odds ratio itself *post hoc*. The Code Committee considered that the BMSA would have been able to calculate the odds ratio based on the data available to the company and could have included this in the forest plot. The Committee also noted that pleural effusion had been included in the bar graph on page 1 of the piece, although this had been referenced to a different source.

The Committee noted that the forest plot was referenced to an oral presentation at the American Society of Hematology (ASH) 2014 annual meeting, not to published data. This issue had not been raised by Novartis in its complaint. The Committee considered that an alternative source or sources for the adverse events odds ratios could have been available to BMSA.

Some members of the Committee noted that the promotional material had been directed to a very specialised sub-set of prescribers, specialist oncologists, who would be familiar with critically interpreting these data. These Committee members also noted that there had been a focus on pleural effusion throughout

the promotional piece. These Committee members' considered that BMSA had not sought to minimise the incidence or seriousness of pleural effusion, however they agreed with the rest of the Committee that it could have been presented and communicated more clearly and was therefore misleading.

The Committee agreed unanimously that the forest plot was misleading due to the omission of pleural effusion from it and therefore was in breach of Section 1.3 of the Code.

Abuse of the Code

The Committee discussed BMSA's allegation of abuse of the Code of Conduct by Novartis. In its response to the complaint, BMSA alleged that Novartis had strategically withheld its complaint until the time of the year when it would be the most disruptive, in the lead up to a large annual clinical conference. BMSA stated that this was the second consecutive year when Novartis had made a complaint against BMSA at the same time.

The Committee had been provided with the reasons for decision for complaint 1126, Sprycel promotional material, which was considered in January 2015. The Committee reviewed the reasons for the decision and noted that the Committee had commented that the previous complaint had lacked detail and that intercompany dialogue could have been more constructive. Some breaches of the Code had been found for this complaint. The Committee agreed that Novartis' complaint submission for the current complaint demonstrated improvement, although its complaints could have been more clearly presented.

The Committee unanimously agreed, however, that it did not consider Novartis' conduct in bringing a further complaint, where breaches of the Code had been found, rose to the level of being frivolous or vexatious.

Sanction

Having found breaches of the Code of Conduct, the Code Committee discussed the severity of these breaches. The Code Committee agreed by unanimous decision that the breaches were moderate as defined in the Code of Conduct. The Committee considered that the promotional materials were misleading and had the potential to alter the way oncologists prescribe the product.

The Committee agreed unanimously that

- The promotional materials must be withdrawn from use and the claims and forest plot found in breach of the Code must not be used again in the same or similar form;
- All promotional materials and/or advertisements containing the claims and/or forest plot found in breach must be withdrawn from use and not used again in the same or similar form.

The Committee also agreed by majority decision that BMSA must pay a fine of $50,000.