

Medicines Australia Code of Conduct Quarterly Report October - December 2007

Medicines Australia Code of Conduct

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 15 (Effective 6 December 2006).

This report covers all complaints finalised between October and December 2007. Complaints finalised during this period were in relation to materials or activities conducted under Editions 14 and 15 of the Code.

Quarterly Reports preceding this Report:

- Quarterly Report 1: January - March 2007 and
- Quarterly Report 2: April - June 2007 were incorporated into the Code of Conduct Annual Report 2007
- Quarterly Report 3: July - September 2007

These reports are also available from the Medicines Australia website.

How to contact Medicines Australia

Address:

Level 1, 16 Napier Close
DEAKIN ACT 2600

Phone: 02 6122 8500

Fax: 02 6282 6299

Email: secretarycodecommittee@medicinesaustralia.com.au

How do I obtain a copy of the Code?

Hard copies of Edition 15 of the Code are available from Medicines Australia.

The Code of Conduct and the Guidelines that accompany the Code are available from the website (www.medicinesaustralia.com.au).

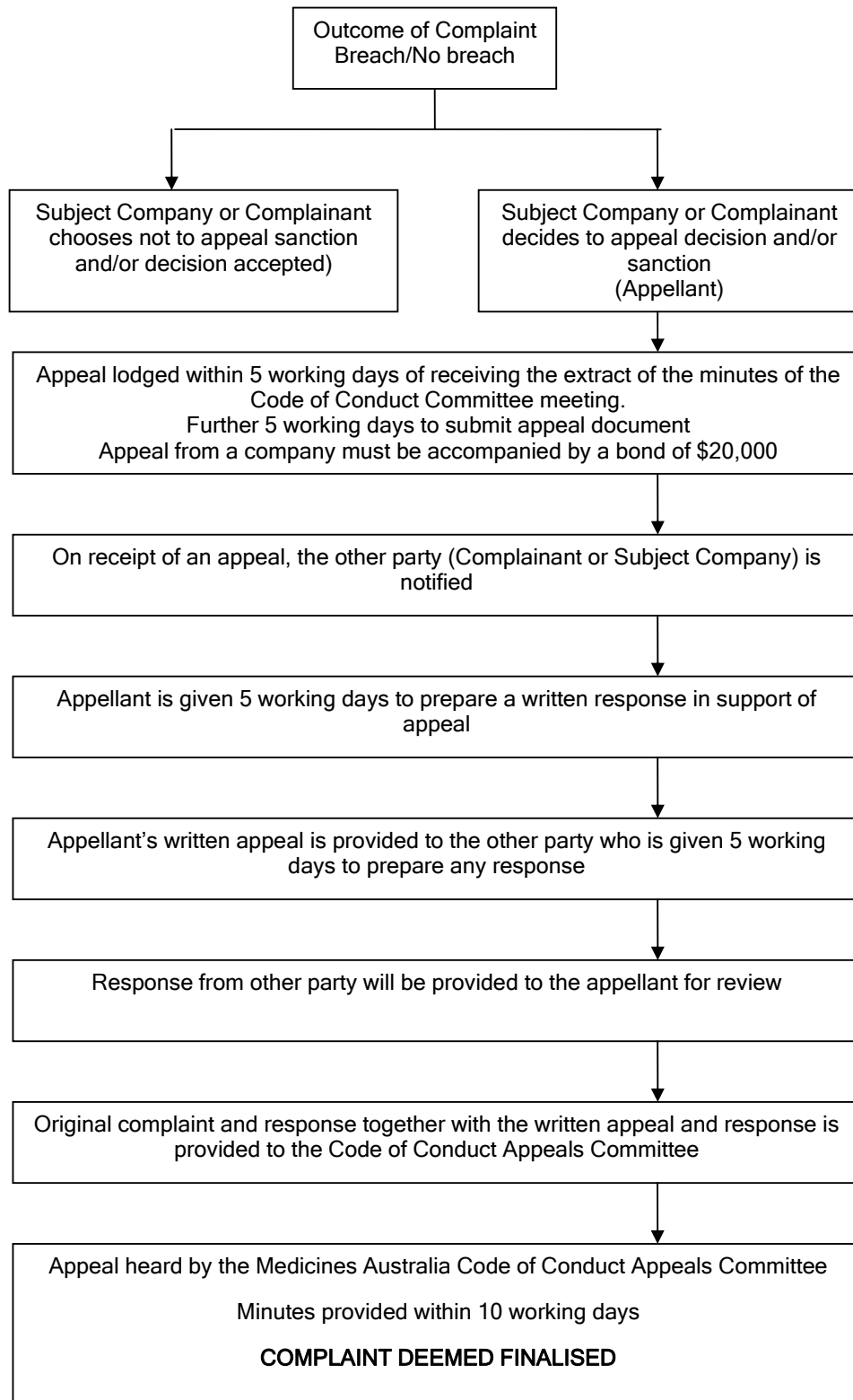
Contents

	Page
Medicines Australia Code of Conduct Complaints Handling Process	3
Medicines Australia Appeals Committee Procedures	4
Code of Conduct and Appeals Committees	5
Sanctions which can be imposed by the Code of Conduct Committee	6
Finalised Complaints:	7
Roche Media Releases 872	
Actonel 877	
Femara 878	
Seretide 879	
Famvir 880	

Medicines Australia Code of Conduct Complaints Handling Process



Medicines Australia Code of Conduct Appeals Committee Procedures



Medicines Australia Code of Conduct and Appeals Committees

Complaints listed in this report were considered by the following Committees:

Code of Conduct Committee

Full Members	Observers (No voting rights)
Independent lawyer (Chair)	Two employees of Medicines Australia Member Companies *
One representative nominated by the following organisations:	An observer interested in the Code process
Australian Divisions of General Practice (ADGP)	
Australian Medical Association (AMA)	
Australian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT)	
Consumers' Health Forum of Australia	
Royal Australasian College of Physicians (RACP)	
Royal Australian College of General Practitioners (RACGP)	Advisors (No voting rights)
Therapeutic Goods Administration (TGA)	Code of Conduct Secretary
3 Medicines Australia Association Representatives *	Medicines Australia officer responsible for Scientific and Technical Affairs
2 Medicines Australia Medical/Scientific Directors *	Medicines Australia Chief Executive Officer or delegate

Code of Conduct Appeals Committee

Full Members	Advisors (no voting rights)
Independent lawyer (Chair)	Code of Conduct Secretary
Representative from the target audience to which the promotional activity has been directed e.g. RACGP, AMA, ADGP	Medicines Australia Chief Executive Officer or delegate
Representative from the Australian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT)	
Representative from the College and/or Society from the therapeutic class of the product	
Representative from the Consumers' Health Forum of Australia	
2 Medicines Australia Association Representatives *	
Medicines Australia member company Medical/Scientific Director *	

* Medicines Australia representatives on either Committee must not have a conflict of interest with the therapeutic class of the materials being reviewed.

Sanctions which 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.

Fine

Breach

Technical breach
Minor breach
Moderate
Severe breach

Fine

Maximum of \$100,000

Severe breach where activities have ceased
Breach repetitions
Repeat of previous breach

Maximum of \$200,000

Table of finalised complaints September - December 2007

No.	Subject Company	Material Activity	Product	Complainant	Outcomes*	Sanction
872	Roche	Media releases	N/A	GlaxoSmithKline	No breach 1.5, 9.6, 9.6.1, 9.6.4, 9.10 Breach 1.1, 1.3.1, 9.2.1, 9.2.4, 9.3, 9.4	<ul style="list-style-type: none"> • Remove media releases from website • Fine \$110,000
877	sanofi-aventis	Promotional material	Actonel	Merck Sharpe & Dome	No breach 1.2.1, 1.7, Breach 1.2.2, 1.3	<ul style="list-style-type: none"> • Withdraw • Corrective letter • Fine \$80,000
878	Novartis	Promotional material	Femara	AstraZeneca	No breach 1.2.2, 1.3	N/A
879	GlaxoSmithKline Australia	Promotional material	Seretide	Boehringer Ingelheim & Pfizer Australia	No breach 1.2.2; Breach 1.3, preamble to 3, 3.1.1.3	<ul style="list-style-type: none"> • Withdraw • Fine \$50,000
880	Novartis Pharmaceuticals	Promotional brochure	Famvir	Healthcare Professional	No breach 1.1, 1.2.2, 1.3	N/A

Roche Media Releases 872

Subject Company: Roche Products

Complainant: GlaxoSmithKline Australia (GSKA)

Product: Not applicable

Complaint

GSKA alleged that Roche had made available in Australia over 20 media releases which promoted either unregistered products or unregistered indications for registered products. GSKA alleged that Roche had made these media releases available both directly to the general public via the company website and indirectly through the lay media with the purpose of publication of media articles and promotion of prescription products to the general public.

Sections of the Code

Materials alleged to be in breach of the following Sections of the Code:

- 1.1 Responsibility
- 1.3.1 Unapproved products and indications
- 1.5 Unqualified superlatives
- 9.2 Product Specific Media Statements (including 9.2.1, 9.2.2 and 9.2.3)
- 9.3 General Media Articles
- 9.4 Promotion to the general public
- 9.6 Use of the Internet (including 9.6.4)
- 9.10 Discredit to and reduction of confidence in the Industry

Response

Roche responded that the complaint was unfounded, retrospective and had not followed due process. Roche alleged that the complaint was an abuse of the complaint process and was frivolous and vexatious and therefore in breach of Section 12.3 of the Code.

July Code Committee Decision

After a detailed review of the material provided by GSKA and Roche the Committee determined to defer any decision in relation to the complaint until it has received a more properly formulated complaint from GSKA and Roche has had the opportunity to respond to it. The Committee recognised that the appropriate

communication of landmark clinical information was an important issue and further information would assist it in making a determination. The views of this Committee would assist Medicines Australia and the Code Review Committee in formulating future policy.

August Code Committee Decision

In unanimous decisions the Code Committee found breaches of the Code in relation to three media releases:

Media Release #17 dated 12 December 2006 (Considered under Edition 15 of the Code)

Breach of Sections 1.1, 9.2.1, 9.3 and 9.4 of the Code

Sanctions

- Remove from any public access website and not issue the media release again in the same or similar form
- Fine \$20,000

Media Release #20 dated 20 October 2005 (Considered under Edition 14 of the Code)

Breach of Sections 1.1, 1.3.1, 9.2.1, 9.2.4, 9.3 and 9.4 of the Code

Sanctions

- Remove from any public access website and not issue the media release again in the same or similar form
- Fine \$60,000

Media Release #21 dated 18 May 2005 (Considered under Edition 14 of the Code)

Breach of Sections 1.1, 9.2.1, 9.3 and 9.4 of the Code

No breach of Section 9.10 of the Code

Sanctions

- Remove from any public access website and not issue the media release again in the same or similar form
- Fine \$40,000

The Committee did not find any breach of the Code in relation to media releases numbered 1-16, 18 or 19 as submitted in the complaint.

October Code Committee Decision

In a unanimous decision the Committee found no breach by GSKA of Section 12.3 of the Code.

Consideration of the complaint

The Committee considered several general issues raised by Roche and GSKA in relation to Section 9.2 of the Code.

Do provisions under Section 1 of the Code apply to complaints pertaining to Section 9.2?

Members were of the view that irrespective of medium, that is hard copy, electronic format, computer based, website or available through a media release, it is the responsibility of a company to ensure that the content of all materials produced and/or distributed by it or on its behalf are balanced, factual, correct and not misleading to a reader, whether intended for a healthcare professional, patient or general public audience. It was therefore the Committee's opinion that a complaint in relation to a media release may also be subject to a complaint under provisions such as Sections 1.1 and 1.3 of the Code. This does not mean, however, that Section 9.2 should be interpreted as if it contained language that it does not. In particular, the reference in Section 1.3.1 to unapproved indications should not be imported into Section 9.2.

Does Section 9.2 apply to media activity to communicate or respond to landmark studies in non approved products and landmark studies for approved products in new indications?

Members were of the view that the requirements of Section 9.2 do not permit media releases relating to unapproved products. Contrary to GSKA's suggested interpretation, Section 9.2 regulates the circumstances under which media releases relating to non approved indications may be made. The provisions apply whether a company is proactively distributing a media release about a non approved indication or whether a company is responding to a question about a landmark clinical trial. Any communication must also be considered on the basis of the representation of the outcomes of the study that it refers to - that is, it must be current, accurate, balanced and must not be promotional.

Does the Code hold Australian companies responsible for the content of their parent company's global media/news releases?

Whilst noting that the Australian company is not responsible for the content of parent company media releases, members were of the view that it is the manner in which such a global release is used or distributed within Australia that is considered in reviewing a complaint under the Code, including whether the Australian company actively distributed the global media release in Australia and whether the Australian company directed Australian healthcare professionals to view a new media release on the parent company website.

On the evidence provided to it, the Committee formed the view that Roche had not promoted the global releases to Australian healthcare professionals nor to the general public, although the media releases could be accessed through the Roche Australia website through a link, 'Global News', to the parent company website. Members noted that Roche had included a statement on the Australian website in accordance with Section 9.6.4 advising visitors, prior to leaving the Roche Australia website, that

"The information that you are about to be referred to may not comply with the Australian regulatory environment and that you should refer to the CMI for products to fully understand the terms of a product's registration in Australia; and that the intent of providing this material is informational and not as advice; and any information provided by this source should be discussed with the reader's healthcare professional and does not replace their advice.

[Please see our CMI/PI Download Centre](#)

News from the global Roche Group can be found at the following location.

<http://www.roche.com/med-cor>"

In relation to the global media releases numbered 1-16, 18 and 19, the Committee did not find any breach of the Code as members accepted that Roche had not promoted or distributed the releases within Australia.

Global Media Release #1 dated 22 February 2007 (Edition 15)
No breach of Sections 1.1, 1.3.1, 9.2.1, 9.3, 9.4, 9.6, 9.6.1 or 9.6.4

Global Media Release #2 dated 24 January 2007 (Edition 15)
No breach of Sections 1.1, 1.3.1, 9.2.1, 9.3, 9.4, 9.6, 9.6.1 and 9.6.4

Global Media Release #3 dated 12 December 2006 (Edition 15)
No breach of Sections 1.1, 1.3.1, 9.2.1, 9.3, 9.4, 9.6, 9.6.1 and 9.6.4

Global Media Release #4 dated 11 December 2006 (Edition 15)
No breach of Sections 1.1, 1.3.1, 1.5, 9.2.1, 9.3, 9.4, 9.6, 9.6.1 and 9.6.4

Global Media Release #5 dated 20 November 2006 (Edition 14)
No breach of Sections 1.1, 1.3.1, 1.5, 9.2.1, 9.3, 9.4, 9.6, 9.6.1 and 9.6.4

Global Media Release #6 dated 2 October 2006 (Edition 14)
No breach of Sections 1.1, 1.3.1, 9.2.1, 9.3, 9.4, 9.6, 9.6.1 and 9.6.4

Global Media Release #7 dated 31 July 2006 (Edition 14)
No breach of Sections 1.1, 1.3.1, 1.5, 9.2.1, 9.3, 9.4, 9.6, 9.6.1 and 9.6.4

Global Media Release #8 dated 17 July 2006 (Edition 14)
No breach of Sections 1.1, 1.3.1, 9.2.1, 9.3, 9.4, 9.6, 9.6.1 and 9.6.4

Global Media Release #9 dated 27 June 2006 (Edition 14)
No breach of Sections 1.1, 9.2.1, 9.4, 9.6, 9.6.1 and 9.6.4

Global Media Release #10 dated 22 June 2006 (Edition 14)
No breach of Sections 1.1, 1.3.1, 9.2.1, 9.3, 9.4, 9.6, 9.6.1 and 9.6.4

Global Media Release #11 dated 3 June 2006 (Edition 14)
No breach of Sections 1.1, 9.2.1, 9.3, 9.4, 9.6, 9.6.1 and 9.6.4

Global Media Release #12 dated 29 May 2006 (Edition 14)
No breach of Sections 1.1, 1.3.1, 9.2.1, 9.3, 9.4, 9.6, 9.6.1 and 9.6.4

Global Media Release #13 dated 6 April 2006 (Edition 14)
No breach of Sections 1.1, 1.3.1, 1.5, 9.2.1, 9.3, 9.4, 9.6, 9.6.1 and 9.6.4

Global Media Release #14 dated 26 April 2007 (Edition 15)
No breach of Sections 1.1, 9.2.1, 9.3 and 9.4

Global Media Release #15 dated 22 January 2007 (Edition 15)
No breach of Sections 1.1, 1.3.1, 1.5, 9.2.1, 9.3 and 9.4

Global Media Release #16 dated 14 December 2006 (Edition 15)
No breach of Sections 1.1, 1.3.1, 9.2.1, 9.3 and 9.4

Global Media Release #18 dated 12 November 2006 (Edition 14)
No breach of Sections 1.1, 1.3.1, 9.2.1, 9.3 and 9.4

Global Media Release #19 dated 13 October 2006 (Edition 14)
No breach of Sections 1.1, 1.3.1, 9.2.1, 9.3 and 9.4

In relation to the media releases #17, 20 and 21 dated 12 December 2006, 20 October 2005 and 18 May 2005 respectively the Committee found breaches of the Code as members were of the view that Roche Australia had distributed the releases within Australia and the releases did not comply with the provisions of the Code.

Media Release #17 (12 December 2006 - considered under Edition 15 of the Code)
Some members commented that the media release referred to the results of a clinical trial and there is no evidence that the trial was a 'landmark study'. Members also commented that irrespective of whether it was a 'landmark study' the release concerned a specific medicine and was promotional through the use of terms such as "give hope to thousands...", "results represent a major advance in the treatment...", "definitive proof", "has revolutionised", and "major milestone"; and

did not provide a balanced perspective of the product by omitting information in relation to the precautions, contraindications, warnings etc. Whilst there was a link to the CMI provided in the footnotes in the media release, the Code requires that the information about the product's precautions, adverse reactions contraindications etc must be included in the media release. The Committee was also of the view that statements such as those identified above may encourage a patient to seek to be prescribed the specific prescription-only medicine. The Committee noted that the media release directed members of the general public to "talk to your healthcare professional." The media release was found in breach of Sections 9.2.1 and 9.4 of the Code.

The Committee considered that the purpose of the media release was to encourage publication of general media articles. However in the absence of objective evidence that Roche had taken any action to initiate a general media article other than by issuing the media release subject to complaint, it found no breach of Section 9.3 of the Code.

The Committee found the media release to be in breach of Section 1.1 of the Code because, by the omission of information about the precautions, side effects, warnings and contraindications associated with the product, it was not balanced Roche has a responsibility to ensure that any media release by it or on its behalf is balanced and is not promotional.

Sanctions

Having found a number of breaches of the Code the Committee considered an appropriate sanction.

The Committee determined that Roche should:

- Remove the media release from any public access website and not issue the media release again in the same or similar form
- Pay a fine of \$20,000

Media Release #20 (20 October 2005 - considered under Edition 14 of the Code)

The Committee noted that while the release was issued by the Australian New Zealand

Breast Cancer Trials Group (ANZBCTG), Roche had funded the development and distribution of the media release by ANZBCTG in association with a PR company, although Roche had stated that it did not have any input into the content of the release.

Members expressed the view that if a media release was genuinely independent of a pharmaceutical company there would be no connection with the company that is the sponsor of the product. The Committee considered that although Roche had not had editorial control over the media release, nor any input into the content, it had funded the logistics for the issue of the media release in the knowledge that the ANZBCTG intended issuing the release about the particular clinical trial results. Roche therefore had some responsibility for the media release. The Committee noted that Roche had stated in the 'response' column in its tabulated response that it had not "taken any action to initiate a general media article other than by issuing the media release subject to complaint" (emphasis added), which was understood by the Committee to be an admission by Roche that it had issued the release. In any event, a majority of the Committee was of the view that Roche was responsible for ensuring this release was balanced with regard to its product as the release had been funded by Roche.

The Committee agreed with the arguments proposed by GSKA that the media release was promoting an unapproved use of Herceptin and was therefore in breach of Section 1.3.1. As the media release had been issued to the general media and included a number of promotional statements as had been identified by GSKA, the media release was found to promote Herceptin to members of the general public and was therefore in breach of Section 9.4 of the Code.

The Committee agreed that Roche had been responsible for the initiation of a media release about an unapproved use of a product and was therefore in breach of Section 9.2.1 of the Code. A majority of the Committee determined that Roche was in breach of Section 9.2.4 of the Code because the media release was issued by ANZBCTG, with the assistance of a PR agency, and the

release was funded by Roche, and did not comply with the Code.

For similar reasons to those found in relation to media release #17, the omission of information about the risks associated with Herceptin (precautions, contraindications, side effects and warnings) resulted in a lack of balance. The media release was therefore in breach of Section 1.1 of the Code.

The Committee considered that the purpose of the media release was to encourage publication of general media articles. However in the absence of objective evidence that Roche had taken any action to initiate a general media article other than by issuing the media release subject to complaint, it found no breach of Section 9.3 of the Code.

Sanctions

Having found a number of breaches of the Code the Committee considered an appropriate sanction.

The Committee determined that Roche should:

- Remove the media release from any public access website and not issue it again in the same or similar form
- Pay a fine of \$60,000

In determining that a higher fine should be applied in relation to media release # 20, the Committee considered that Roche had used a third party to communicate promotional information about its product to the general public and had failed to exercise adequate control over organisations it had funded, in the knowledge that the funding provided was going to be used to issue a general media statement that would be favourable to its product.

Media Release #21 (18 May 2005 - considered under Edition 14 of the Code)

Roche had stated that media release #21 was a parent company global release that was provided by Roche to a public website designed to provide information about medical treatments to consumers, the Virtual Cancer Centre. Members were of the view that Roche Australia could have responded to the enquiry for information about studies released at the ASCO meeting otherwise

than by simply providing the parent company media release concerning a non approved indication for a particular prescription medicine. In responding to the request Roche could have provided information that was balanced and not promotional that complied with the Code.

For the same reasons as applied in relation to media releases #17 and #20, the Committee found that the supply of the global media release to the Virtual Cancer Centre for publication on its Australian website was a breach of Sections 1.1 (failure to provide balanced information), 9.2.1 (supply of a media release that is not balanced and which is promotional for a non approved use of a product) and 9.4 (promotion to the general public) of the Code as the company had a responsibility to ensure the information released in Australia is balanced and not promotional. The Committee also considered that Roche had failed to provide appropriate educational material in response to a request and therefore was in breach of Section 9.3 of the Code.

Sanctions

Having found a number of breaches of the Code the Committee considered an appropriate sanction.

The Committee determined that Roche should:

- Remove the media release from any public access website and not issue it again in the same or similar form
- Pay a fine of \$40,000

In a majority decision the Committee did not find a breach of Section 9.8 (Edition 14)/9.10 (Edition 15) of the Code. Members were of the view that of the 21 media releases alleged to be in breach of the Code, findings of a breach had been found in relation to only three releases and that further guidance to companies and future Code of Conduct and Appeals Committees was required in relation to Sections 9.2 and 9.3 of the Code.

The Committee discussed whether Code of Conduct Committee or Medicines Australia should set a time limit for the lodgment of complaints as numerous releases subject to this complaint were released in 2005. This matter will be discussed at a subsequent meeting and forwarded to the Code Review

Panel for consideration when the Code is next revised.

The Committee considered the allegation by Roche that this complaint was an abuse of the complaints process and was frivolous and vexatious. By a majority decision the Committee determined that GSKA should be asked to show cause why the Committee should not impose a fine for abuse of the Code of Conduct.

The Committee also considered the allegation from Roche that it had been denied procedural fairness by GSKA in the processing of the complaint. The Committee determined that since the last meeting of the Committee Roche had had the opportunity to provide and had provided a full defense to the allegations and had been afforded sufficient time to recover its position if any procedural disadvantage had actually occurred.

Appeals Committee

Roche lodged an appeal against some of the decisions of the Code Committee. Roche stated that the core issue was whether the reference to an unapproved indication is prohibited in media releases concerning major developments such as landmark studies concerning approved products. The central issue in the appeal is the correct interpretation and application of Sections 9.2 and 9.3 to media releases and how they relate to Section 1 of the Code.

Appeals Committee Determination

Media Release #17 dated 12 December 2006 (Considered under Edition 15 of the Code)

Breach of Sections 1.1, 9.2.1, and 9.4 of the Code confirmed by unanimous decisions.

Sanctions

- Remove from any public access website over which Roche Australia has control and not issue the media release again in the same or similar form.
- Fine amended to \$30,000

Media Release #20 dated 20 October 2005 (Considered under Edition 14 of the Code)

Breach of Sections 1.1, 1.3.1, 9.2.1, 9.2.4, and 9.4 of the Code confirmed by unanimous decisions.

Sanctions

- Remove from any public access website over which Roche Australia has control and not issue the media release again in the same or similar form. Endeavour to remove the media release from any other website that makes it available to the public.
- Fine amended to \$40,000

Media Release #21 dated 18 May 2005 (Considered under Edition 14 of the Code)

Breach of Sections 1.1, 9.2.1, 9.3 and 9.4 of the Code confirmed by unanimous decisions.

Sanctions

- Remove from any public access website over which Roche Australia has control and not issue the media release again in the same or similar form. Endeavour to remove the media release from any other website that makes it available to the public.
- Fine retained at \$40,000

Consideration of the appeal

The following summarises the main points presented by Roche representatives in favour of its appeal:

Roche appealed all findings of breach of the Code in relation to media releases numbered 17, 20 and 21 in the complaint and the sanctions imposed, which Roche interpreted as being reflective of the number of breaches found

- All three media released were issued in response to enquiries about key international developments
- All three media releases were about significant improvements in overall survival in cancer - outcomes with clinical impact
- All qualify as 'landmark' studies
- All properly fall within the example in the Explanatory Notes for Section 9
- All studies referenced in the media releases were Phase III studies - Level II evidence (NHMRC hierarchy of evidence)
- Media releases #17 and #21 related to approved indications for the two medicines - non-Hodgkin's Lymphoma and metastatic breast cancer

- Release #20 related to a study that was the basis for approval of new indications for adjuvant breast cancer treatment
- Roche considers the information provided was accurate, balanced, appropriate in the circumstances, and was about study results and not promotional of a product.

Roche considered the most pertinent Section of the Code relevant to the media releases was Section 9: Relationship with the General Public. Under this section, industry may provide information about medicines and studies, as long as proper standards are observed, which are documented in Section 9. The Explanatory Note identifies key developments including landmark studies as an exceptional circumstance in terms of section 9.2

In relation to proper interpretation of Section 9.2.1:

- Media releases are permitted to announce a new product or major indication approval for medicines available in Australia
- Such releases must include the product's precautions, adverse reactions, warnings, contraindications and interactions

However, the releases in question were not announcing availability of new products or indications, so Section 9.2 doesn't apply, in Roche's opinion, and also do not fall under Sections 9.3 or 9.4. Roche argued that if 9.2 did apply to a media release about a study, this would mean that the release would have to include warnings, precautions, contraindications etc about every drug in the study, which, in their view, is unreasonable.

Roche did not agree that it is the intention of the Explanatory Notes to Section 9.2, in specifically allowing a media statement about a key development such as a landmark study, to then have such a release condemned as a breach of Section 9.4 that prohibits product promotion to the general public.

Roche did not agree that Section 1 should be applied to these media releases.

- The principles in Section 1 are only relevant to promotional and medical claims about products
- The releases were not about product specific promotional claims and therefore do not fall under Section 1 or 1.3.1

Roche referred to the requirement in Section 9.2.1 that a media release must be in language that reflects current community standards. In support of their position that the language was not promotional Roche stated that the language used in the media releases was consistent with that used by:

- Investigators and collaborative groups
 - Independent clinical experts
 - The media
 - Other companies
- when publicizing positive study results.

Roche cited statements from several sources as evidence to support their position that the language in the media releases was consistent with language used to describe the impact of the studies in the clinical arena, an internationally renowned expert oncologist; a *New England Journal of Medicine* (NEJM) editorial and the high level of media interest in the study results.

In relation to the Australian New Zealand Breast Cancer Treatment Group (ANZBCTG) media release (#20), that Group had initiated the request for sponsorship from Roche for the media release. The release related to a US study which was not sponsored by Roche Australia. There was no pre-existing relationship with ANZBCTG in relation to the NEJM publication. ANZBCTG's interest was not in promoting a particular product but was to promote its involvement in important international studies, the value of patients participating in clinical trials, and positive clinical outcomes for patients. Roche referred to statements in the media release which were found to be promotional of Roche's product, which Roche considered were about the study concerned, not the product.

Roche considered that the finding of breaches for the ANZBCTG release as though the Treatment Group was acting as an agency for Roche was contrary to the fact that Roche had no involvement in the media

release. The release contained statements by a third party about study results which had been wrongly interpreted as company promotion of an unapproved indication, despite the Code stating that landmark studies can involve new indications. Roche further objected to the \$60,000 sanction imposed for ANZBCTG's language, which is higher than that imposed for a breach where a company was directly publicising an unapproved product (Complaint 867).

In relation to media release #17, Roche explained that survival rates for patients with non-Hodgkin's Lymphoma (NHL) have not changed for decades. The study referred to in the media release was the earliest study to show significant overall survival benefit of treatment with rituximab first line in follicular NHL. Information about the study which was presented at the American Society of Haematology (ASH) meeting was requested by a number of Australian organisations, including the Leukaemia Foundation Australia and Lymphoma Support and Research Association. Media release #17 was placed on the Roche Australia website in a password protected area accessible by healthcare professionals and patients already prescribed rituximab and was issued to the media.

Roche maintained that the positive statements identified by the Code Committee as the basis for finding the media release in breach of the Code relate to results of the study, not the drug itself. Roche did not agree that the media release was product promotional.

In relation to media release # 21, which appeared on the Virtual Cancer Centre (VCC) website, Roche had provided the global release to the VCC, and in hindsight recognised that it would have been preferable to only provide information about the study. In defense of the conduct, the release was from May 2005; the release provided information about the reported study which was factual and not misleading and related to an approved indication for the medicine. Roche considered that there would be minimal consequences for patients because the medicine can only be prescribed by a specialist medical practitioner.

In relation to sanctions, Roche submitted that the penalties were too severe and should be substantially moderated. Positive language in the media releases is about the studies, not the products. Some releases raised in the complaint were more than two years old and no complaints had been raised in that time. Roche had no information or advice that the releases were not acceptable. If it had been aware, Roche would have changed its conduct. The sanction of \$120,000 is inconsistent with that imposed in complaint 867 for which GSK had been found in breach for publicising an unapproved product.

The Code Committee erred in stating breaches of Section 9.3 of the Code were found when determining the sanctions.

GSKA presentation

The following summarises the main points presented by GSKA representatives: Media releases are common. GSK has identified 30 media releases issued by 8 companies in the two-year period to March 2007. 21 referred to an unapproved product or indication; 16 were issued by a single company.

GSKA noted that the Code Committee has considered 3 complaints about media releases in 2007 (867, 871, 872). The Code Committee had recognised some potential interpretive inconsistencies between provisions of the Code and the Explanatory Notes in Sections 9.2 and 9.3. The Committee had endeavoured in great detail to clarify interpretation of the Code to provide assistance to companies in complying with the Code and had referred these differences to the next Code Review Panel. The Committee had confirmed that the provisions of the Code take precedence over the Explanatory Notes.

In its consideration of Complaint 867, the Code Committee made clear that media releases about unapproved products are not acceptable and cannot be initiated by a pharmaceutical company; releases cannot have promotional content and must be balanced through provision of information on side effects, precautions, contraindications etc. The Code Committee can only respond to evidence presented to it on the actual content of media releases.

In complaint 871, there was media coverage in the absence of a media release; the complaint dealt with responding to media enquiries.

GSKA noted that in the current complaint (872), in relation to eighteen media releases, which were all global media releases only available on a global company website, the Code Committee had determined that an Australian subsidiary has no responsibility unless such releases are distributed by the company in Australia.

GSKA agreed with the Code Committee that media release #17 was in breach of the Code. GSKA considers that study results are the basis for all promotional claims that a company makes. Thus it cannot be argued that information about study results cannot be product promotional. For media release #20, GSKA agreed that a pharmaceutical company has responsibility for media releases issued by a third party organisation or agencies that it has sponsored to undertake that activity. The ANZBCTG release promoted an unapproved indication of a registered product to the general public. Media release #21 included promotional content for an unapproved indication of a registered product. Consideration of this release highlighted what should be an appropriate response to media enquiries.

GSKA concluded that Sections 1 and 9 of the Code are fundamental to what can and cannot be promoted to health professionals and the general public. Section 9 deals with companies' relationship with the general public, highlighting a higher onus of responsibility and a higher standard for provision of balanced information. GSKA proposed that the decisions of the Code Committee in Complaints 867, 871 and 872 have substantially increased clarity about Sections 1 and 9.

GSKA considered that the Code Committee's decisions in relation to complaint 872 provide an appropriate framework for companies in relation to media releases. Therefore, the decisions in complaint 872 should be confirmed and the appeal should be rejected. The sanctions imposed are based on relevant precedents and are appropriate.

Following GSKA's presentation the Appeals Committee sought clarification on several matters:

The Chairman invited Roche to further elaborate on its argument that the Code Committee cannot find a breach of two sections of the Code in relation to media releases and why Roche considered that a media release was not subject to Section 1. GSKA representatives responded that Roche had interpreted the Code Committee reasoning to be that because the precautions, contraindications etc had not been included in the media releases they were in breach of 9.2 and that the releases were therefore not balanced and in breach of Section 1.1. Roche considered that the statements in the media releases were about clinical studies, were fair, factual, balanced and were not promotional statements. The Chairman responded that Section 9 is a narrower prohibition on conduct than Section 1, but both can apply to media releases.

A Committee member questioned Roche about the appropriate interpretation of different contexts in which information about study results is discussed. He noted that some of the media releases related to study results discussed at a conference but not published at the time. Sometimes what is presented at a conference is more positive than the subsequently published paper following peer review, which is the reason the Code does not accept abstracts and posters as the sole basis to support claims. There is also a different interpretive context between an investigator presenting results to professional colleagues and communicating the results to the general public, noting that a lay person would not share the same understanding as a learned audience. Roche responded that the minutes of the Code Committee record particular phrases from the media releases out of context and concluded they were promotional. Roche maintained that the language in the media releases was to describe the studies, not the products. The releases were not found to be inaccurate, or to have misled physicians. Roche considered that the language used in the media releases is consistent with that used in presenting results at a conference.

The Chairman questioned Roche about the terms of Section 9 as it applies to the media releases. He proposed that Sections 9.2 and 9.3 should be interpreted as a prohibition on certain conduct in relation to media releases and identify a distinction between what may be initiated by companies and when companies may only respond to an enquiry. It could be said that media releases are initiating communication. Roche responded that in each case the company was responding - people in different organisations and groups had asked Roche to respond to information about major issues that arose at ASH or the American Society of Clinical Oncology (ASCO) meetings. Roche stated that if the Australian media want to publish a story they will seek an opinion from an expert. The Chairman suggested that there are ways of responding to a request for information other than issuing a media release.

Roche then made its concluding remarks. Roche noted that it shared the perspective with GSKA that there had been lack of clarity in the Code, which is the reference point for decisions on the acceptability of certain conduct. Roche believed it had made a reasonable interpretation of what was acceptable. The complaints referred to by GSKA had all occurred since February 2007 - none of that information was available to Roche when the media releases were issued.

Roche believed that the Code Committee had made subjective interpretations of language in the media releases and concluded that certain statements were promotional. Studies that were the subject of the media releases included reference to unapproved indications, but the Code, in Roche's view, recognised that information on unapproved uses was valid.

The releases posed no threats to patient safety - Roche believed that patients with cancer can't demand a prescription for MabThera or Herceptin on the basis of a media release or media story. The impact of the releases doesn't warrant the sanctions imposed.

The GSK and Roche representatives left the meeting following these presentations.

The Committee unanimously agreed that Section 1 of the Code does apply to media releases - it is broader than Section 9, but does apply.

The Committee considered Section 9.2 of the Code. It considered that the section provides clear language that media releases must be current, accurate balanced and must not be promotional. The explanatory notes to section 9 are for guidance and do not override these requirements of clause 9.2. The Committee determined that the three media releases in question were product specific and promotional. It did not accept Roche's argument that the releases were solely about clinical studies. The language used in the media releases was promotional of the products concerned.

In relation to media release #20, issued by the ANZBCTG, whilst it was written by a third party, Roche had provided sponsorship for the production and issue of the release and therefore must take responsibility for the release. Roche had been aware that the release was to be produced and its subject matter, although Roche had not exercised editorial control, and had funded the ANZBCTG for the specific purpose of issuing the media release. The Committee considered that Roche had an ultimate responsibility for the fact that a media release had been issued. In forming its opinion the Appeals Committee did not rely on the statement in the Code Committee minutes that it understood that Roche had also issued the media release itself. Nonetheless, the Committee determined that Roche had responsibility for the media release.

The Committee reviewed the release and confirmed its view that the media release was about the product, Herceptin, not solely about the study published in the NEJM and was promotional. The Committee also noted that the NEJM publication of the study refers to adverse effects such as cardiotoxicity, which was not mentioned in the media release. The Committee also did not accept Roche's assertion that members of the public with breast cancer would not ask their doctor to prescribe the drug for them after reading media articles. Consumers may not have the same capacity as a health professional to interpret study results.

The Appeals Committee considered that the media releases were promotional. They included statements from key opinion leaders conveying positive attributes of particular medicines arising from clinical studies. The Committee noted that there is a difference between comments in a peer reviewed publication and positive statements by commentators included in a media release. It further noted that further interpretation of study results presented at a scientific conference often occurs during the peer review process prior to publication.

Any response to an enquiry about information about recent clinical studies needs to be confined to being a reflection of the trial itself and put into context of existing information about the medicine used in the trial to provide appropriate balancing information, such as the precautions, warnings, contraindications etc. Publication of a media release containing third party commentary is not regarded as the company responding to an enquiry but is rather drawing attention to that third party's response to an issue, and can be regarded as promotional.

The Appeals Committee concluded that Roche had not persuaded it that the Code Committee had erred in its findings. The Appeals Committee confirmed the determinations of the Code of Conduct Committee in relation to all three media releases (#17, #20 and #21).

The Appeals Committee advised that an appropriate disclaimer of a website page that links to a global website which may not comply with Australian Code of Conduct requirements should be maintained. It should be clear to a reader that the information available from the linked page may not comply with Australian requirements. It would also be beneficial to provide a further notice on the global webpage.

Sanctions

Having not upheld the appeal the Appeals Committee considered the sanctions imposed by the Code of Conduct Committee.

Media Release #17 dated 12 December 2006 (Considered under Edition 15 of the Code)

- Remove from any public access website over which Roche Australia has control and not issue the media release again in the same or similar form.
- Fine amended to \$30,000. In increasing the fine from \$20,000 to \$30,000 the Committee determined that the language contained in the media release was more culpable than the other two media releases. The activity was also more recent than releases #20 and #21.

Media Release #20 dated 20 October 2005 (Considered under Edition 14 of the Code)

- Remove from any public access website over which Roche Australia has control and not issue the media release again in the same or similar form. Endeavour to remove the media release from any other website that makes it available to the public.
- Fine amended to \$40,000. In reducing the fine from \$60,000 the Committee considered that whilst the issues subject to complaint were essentially the same as the other two media releases, the involvement of a third party in issuing the media release justified a higher fine than that imposed in relation to media release #17.

Media Release #21 dated 18 May 2005 (Considered under Edition 14 of the Code)

- Remove from any public access website over which Roche Australia has control and not issue the media release again in the same or similar form. Endeavour to remove the media release from any other website that makes it available to the public.
- Fine retained at \$40,000. The Appeals Committee determined that whilst the issues subject to complaint were essentially the same as the other two media releases, the breach was broader, including Section 9.3 of the Code. Further, there was no lack of clarity in relation to the requirements of Section 9.3, as has been suggested in relation to Section 9.2. Roche should have been more clearly aware of their obligations.

In determining the sanctions, the Appeals Committee specifically stated that the sanctions were not applied simply because there were multiple breaches of the Code found, but on the basis of the totality of the conduct. The penalties applied are lower than might otherwise have been imposed because at the time the conduct occurred Roche could not have been aware of recent decisions of the Code of Conduct Committee for other complaints which would have provided further guidance regarding appropriate and acceptable conduct with respect to media releases.

The Appeals Committee confirmed that Section 9.2 applies to both unapproved products and unapproved indications for approved products.

October Code Committee consideration of a potential breach of Section 12.3

The substantive issues in relation to the complaint by GSKA pertaining to Roche Media Releases 872 had been dealt with by preceding Code of Conduct and Appeals Committees and were not for further consideration.

The Committee considered the response from GSKA to the question whether it had engaged in vexatious conduct. GSKA had expressed surprise to be asked to respond to the breach of Section 12.3 of the Code. GSKA had stated that the outcome from the Tykerb complaint (complaint 867) in their view had set a precedent for interpretation of the Code in relation to the publication of media releases. Having received the minutes pertaining to Tykerb 867, GSKA lodged the complaint against Roche in relation to its media releases to seek further clarification on this matter. GSKA also drew attention to the fact that the Code of Conduct and Appeals Committees had supported GSKA's views in relation to three Roche media statements released in Australia, with substantial financial sanctions being imposed by the Code of Conduct Committee and confirmed with minor amendment by the Appeals Committee.

The Committee considered the Oxford dictionary definitions of 'vexatious' and 'frivolous' and also noted that GSKA had

identified five ways in which a complaint may give rise to concerns that it is vexatious.

Vexation - Causing vexation (annoying, irritating, distressing) and lacking sufficient grounds for action and seeking only to annoy defendant"

Frivolous - not serious, shallow, silly, trifling

Members were unanimous in their view that the complaint was not frivolous.

The Committee also noted GSKA's assertion that the issue of media releases is important for pharmaceutical companies and for the Code of Conduct. GSKA had submitted that they had accepted the decision of the Code Committee in relation to complaint 867 and had not appealed the decision. As a result of the consideration of complaints Tykerb 867, Tykerb 871 and Roche Media Releases 872 the intent and effect of Section 9 of the Code is now much clearer.

The Committee commented that in relation to intercompany dialogue, there had been interactions between GSKA and Roche, however it appeared there were fundamental and unresolvable differences between them. Some members were of the view that there appeared to have been faults on both sides and the matter of vexatious conduct by GSKA, although raised by Roche seemed to lack support.

Members commented that it was difficult to prove intent by GSKA. The Committee noted the e-mail on 1 August 2007 from GSKA to Code of Conduct Secretary, which accompanied the revised complaint. This correspondence provided a contemporaneous view of GSKA's intention in submitting the complaint; that is, to clarify interpretation of the Code, which is consistent with its response to the question of a breach of Section 12.3.

In relation to the amount of information submitted by GSKA in its complaint and whether this was burdensome on Roche, the Committee noted that the July Code of Conduct Committee had requested further information from GSKA and the Secretariat had proposed to GSKA that it set out the revised complaint in a table, identifying each media release alleged to be in breach of the Code, the sections of the Code and the

reasons supporting the allegations of breach of the Code. It was noted that GSKA had a legitimate right to complain, even though the complaint material was substantial. It is not unusual for a complainant to allege breaches of a number of different sections of the Code for a particular activity.

In summarising its reasoning, members agreed that companies have a legitimate right to complain, however they must follow the processes set out in the Code and Guidelines. There were faults by both GSKA and Roche in the intercompany dialogue process and more genuine efforts could have been made to resolve the differences between the companies. In considering the importance of clarifying the use of media releases pertaining to prescription medicines (whether unapproved products or unapproved indications) members were of the view that the three complaints (867, 871 and 872) and the appeal in relation to 872 have resulted in a greater clarity for companies of what is permissible under the Code. Whilst the 872 complaint had been voluminous, GSKA had been invited by the Secretariat to reformulate its complaint in a detailed tabular form.

Code Committee Decision

In a unanimous decision the Committee found no breach of Section 12.3 of the Code by GSKA.

Actonel 877

Subject Company: sanofi-aventis

Complainant: Merck Sharp & Dohme Australia (MSDA)

Product: Actonel

Complaint

The complainant alleged that a sanofi-aventis detail aid failed to make appropriate disclosure of the limitations of the data presented and made significant claims of superiority based on a retrospective observational study.

Sections of the Code

Materials alleged to be in breach of the following Sections of the Code:

- 1.2.1 Provision of Substantiating Data
- 1.2.2 Level of Substantiating Data
- 1.3 False or Misleading Claims
- 1.7 Comparative Statements

Response

Sanofi-aventis denied any breach of the Code and responded that the data were taken from the REAL study which is a robust study with rigorous methodological design that includes full methodological explanations of any potential bias within the published results and can withstand scrutiny in this regard. Sanofi-aventis argued that it would be inappropriate to dismiss the data simply because it was an observational study.

Code Committee Decision

There were three matters before the Committee that had not been resolved through intercompany dialogue.

In relation to the unresolved item 3.1 in the complaint the Committee found a breach of Section 1.3 of the Code by unanimous decision.

In relation to the unresolved item 3.5 in the complaint the Committee found a breach of Section 1.3 of the Code by unanimous decision.

In relation to the unresolved item 3.8 in the complaint the Committee found a breach of

Sections 1.2.2 and 1.3 of the Code by unanimous decision.

Sanctions

- Withdraw materials found in breach
- Fine \$100,000
- Corrective letter to all General Practitioners

Consideration of the complaint

The Committee noted that many of the issues raised in the original complaint had been resolved during intercompany dialogue and only three matters remained unresolved that had been referred to the Committee. However the Committee expressed some reservations about what was agreed to by both parties and the allegations by sanofi-aventis that MSDA had later rescinded their agreement.

Item 3.1 in complaint - Graphs representing non vertebral data for Fosamax (Alendronate) and Actonel

Members were concerned that the graphs had been adapted from the data in the studies and did not provide a healthcare professional with any information about the different patient populations or trial designs. Members also commented that a healthcare professional may not be aware of whether the evidence was the best available data for both products or had been selectively chosen to highlight a difference which is not consistent with the body of evidence.

The Committee found a breach of Section 1.3 of the Code because the graphs on sequential pages of the detail aid were presented in a manner that invites comparison and suggested that the two studies are directly comparable. It was not clear to a reader that the two studies were not head to head comparisons nor that the patient populations and trial designs were different. The presentation was therefore misleading.

Item 3.5 in the complaint - "Actonel reduces the risk of hip fracture by 60% in women with established osteoporosis"

The Committee considered that the graph depicted a selected sub set of the study population - elderly women with confirmed osteoporosis identified by having a vertebral fracture at baseline - but it was not clear to a reader that the results depicted did not

reflect the total study population. The graph did not include confidence intervals which would assist a reader to appropriately interpret the information appropriately. In creating figures using data adapted from a published paper companies must ensure they accurately reflect the findings and include sufficient information to enable correct interpretation such as confidence intervals. Some members were of the view that if a company truly wanted to provide accurate information it would have included the actual table from the published study. Members also commented that the claims under the graph did not accurately reflect the study outcomes and generalised the results from a particular subset of subjects as though they were representative of the total study population, which was misleading.

The Committee found a breach of Section 1.3 of the Code as the information was misleading as it did not fully or accurately reflect the outcomes of the referenced study which stated that *“Risedronate significantly reduces the risk of hip fractures among elderly women with confirmed osteoporosis but not among elderly women selected primarily on the basis of risk factors other than low bone mineral density.”* It was noted that the study population consisted of 5445 women between 70 and 79 and 3886 women aged at least 80 years who met a defined criteria. The results depicted in the graph did not represent the full study population of over 9,000 women.

Item 3.8 in the complaint - REAL study - quote, claims and statements based on the results of the REAL Study

The Committee was of the view that there was some risk in using the REAL study as the basis for making high level comparative claims that imply Risedronate is superior to Alendronate in all circumstances. There is insufficient information presented to healthcare professionals in the detail aid to allow them to make an informed decision of the true comparison between products. Whilst the REAL study provided some favourable comparison for Actonel, the Committee noted that at least one editorial (Ferrari et al) suggested the REAL study was not consistent with randomised controlled trials which had shown comparable efficacy between Actonel and Fosamax.

The Committee found a breach of Sections 1.2.2 and 1.3 of the Code.

Sanctions

Having found a number of breaches of the Code the Committee considered an appropriate sanction. The Committee considered that this was a moderate breach of the Code that was likely to have an effect on how the medical profession would prescribe the product.

The Committee determined that sanofi-aventis should:

- Withdraw the Detail Aid found in breach
- Send a Corrective letter to all General Practitioners informing them that at present there are inadequate data to differentiate between risedronate and alendronate. The content of this corrective letter must be approved by the Committee prior to distribution.
- Pay a fine of \$100,000

Appeals Committee

Sanofi-aventis lodged an appeal against some of the Code Committee's findings. Sanofi-aventis considered that there had been inconsistencies between the specific complaints lodged by MSDA and the basis of the Code Committee's rulings. In the company's view the Committee did not appreciate that the comparative claims for the efficacy of Actonel all related specifically to fracture risk reduction within the first 12 months. Additionally, sanofi-aventis argued that the sanctions were too great for a moderate breach and appeared inconsistent with other decisions. It also claimed that the Committee had not taken into account that the detail aid was withdrawn to implement all changes that were agreed as recorded in the intercompany dialogue minutes.

Sanofi-aventis stated that it would be inappropriate to dismiss the REAL study merely on the basis that it was an observational study and that MSDA should not rely on a generic allegation that observational studies are insufficient to support comparative claims. The study had dealt with the potential for confounding bias and is consistent with the body of evidence.

Sanofi-aventis considered that the presentation of the graphs from the individual randomised controlled trials was

clear and presented in a manner that avoided any confusion or suggestion that they were directly comparative. Sanofi-aventis also stated that the claims are an accurate reflection of the REAL Study and consistent with the body of evidence.

MSDA Response to Appeal

MSDA stated that the use of the REAL Study results as a basis for significant claims of superiority was not justified. The limitations of this retrospective observational study do not permit the claims to be made, especially when they are not consistent with the randomised controlled trials.

MSDA also responded that it had not been aware that the detail aid was no longer being used because the letter from sanofi-aventis informing them of its withdrawal was received after the complaint had been lodged. The fact that it had been withdrawn did not remedy that the breach had already occurred. MSDA further stated that the fine imposed by the Committee was within the range available to them.

Appeals Committee Determination

- In relation to item 3.1 in the complaint the Committee did not uphold the appeal in relation to the breach of Section 1.3 of the Code by unanimous decision.
- In relation to item 3.5 in the complaint the Committee did not uphold the appeal in relation to the breach of Section 1.3 of the Code by unanimous decision.
- In relation to item 3.8 in the complaint the Committee did not uphold the appeal in relation to the breach of Sections 1.2.2 and 1.3 of the Code by unanimous decision.

Sanctions

- Withdraw materials found in breach
- Fine reduced to \$80,000
- Corrective letter to all General Practitioners who had been detailed with the detail aid found in breach of the Code.

Consideration of the Appeal

The following outlines the appeal presentation made by sanofi-aventis:

- Some of the Committee's rationale and findings were inconsistent with the claims

being made and supporting evidence provided

- The promotional piece specifically promotes the early (6 months) reduction in fracture risk with risedronate in post menopausal women, but the Code Committee minutes did not record this critical element to understanding the context of the promotion.
- The promotional piece specifically highlights this distinguishing effect of risedronate through comparison with alendronate utilising randomised controlled trials (RCTs) and an observational study
- The graphs pertaining to non-vertebral data for alendronate and risedronate were on separate pages, were clearly annotated as each being against placebo controls and contained a brief description of the study under the graph with references. The presentation would not lead a healthcare professional into believing that the graphs represented a head to head comparison.
- The Code does not prohibit comparison between non-head to head data
- The Code Committee had found that the REAL study was not consistent with the body of evidence. Sanofi-aventis contended that the detail aid represents the combined data from the pivotal RCTs for each of the drugs for reduction of risk of fracture at 6 months. The validity of these data had not been questioned by MSDA
- sanofi-aventis was not claiming superiority for risedronate in all circumstances, only superior fracture risk reduction at 6 months, which was the context of the promotional piece as a whole
- sanofi-aventis had agreed to modify the title of the graph presenting the REAL study data in intercompany dialogue.
- The Code does not prohibit use of observational studies as supportive evidence
- The REAL study was described in the detail aid as 'complements' RCT in early fracture risk reduction. The claims were consistent with the RCTs; the body of evidence for this endpoint.
- In relation to the graph presenting results from the Hip Intervention Program (HIP) study, the associated claim accurately

reflects the authors' conclusion for the relevant predefined subpopulation of patients.

- Other patients enrolled were outside the approved indications. The claim based on the sub-population analysis is relevant to the approved indications and PBS listings.
- There is sufficient information provided with the graph for a healthcare professional to understand the implications of the data:
 - Graph includes description of subgroup
 - Graph includes the "n-value" of subgroup
- However, given the potential for the reference to the full study population under the graph, 9000 to be misleading, sanofi-aventis agreed to the changes as stated in the minutes of the teleconference with MSDA dated 31 May 2007. Sanofi-aventis considered the matter resolved prior to lodgment of the complaint.

Sanofi-aventis summarised the appeal as follows:

- Appeal relates to a number of critical flaws in the findings of the Code Committee, specifically:
 - The data referenced in the detail aid support the specific claim that risedronate has demonstrated a fracture risk reduction benefit at 6 months whereas alendronate has not
 - This specific claim is entirely consistent with the body of evidence
 - The data representation provides adequate information to enable correct interpretation by professionally trained clinicians
 - Nevertheless sanofi-aventis appreciates potential interpretative concerns with the representation of the data and agreed to implement mutually agreed resolutions
 - sanofi-aventis questions the Committee's findings and the justification for the sanction imposed.

The following outlines the presentation in response to the appeal by MSDA

- The detail aid:
 - As a whole failed to adequately disclose the limitations of the results from the REAL study
 - Significant medical claims for superiority of risedronate were made on the basis of data from a study that was inadequate in design to support these claims
 - There was insufficient information in the detail aid to allow an informed decision regarding the true comparison of efficacy between the two products
- The fact that the graphs on non-vertebral fracture risk were on sequential pages doesn't mean that a comparison between risedronate and alendronate wasn't invited. The detail aid invited comparison by:
 - Identical presentation of the risedronate and alendronate graphs
 - Colour, format, font etc identical
 - Presented on sequential pages - easily switch between one graph to the next
 - Headings invite comparison
- Footnotes beneath the graphs were inadequate to inform a reader of important differences between the studies such that they are not directly comparable - different patient populations and study designs.
- The study referenced in the alendronate graph used 5mg for two years and then increased to 10mg dose. This dosage regimen is not optimal to study the onset of effect in fracture risk reduction and was therefore not a fair comparison.

HIP study graph

- In relation to the HIP study, the graph displaying 60% relative risk reduction appeared under a general heading about hip fractures, with a dot point below that refers to the full study population.
- The qualifying statement below the graph was inadequate in size, but this was resolved in intercompany dialogue.
- There was a 28% relative risk reduction in the total study population; 60% reduction was seen in a sub-population who had a fracture a baseline. It is inevitable that a different patient

population will achieve different outcomes.

- The presentation of the HIP data was not full or accurate.
- The REAL study data do not meet Code requirements for “unequivocal” and “highest quality” evidence to substantiate claims
- Efficacy results from the retrospective, observational REAL study were not consistent with RCT data
- Design and other specific limitations of REAL study mean that the study cannot demonstrate whether there are real differences in efficacy between the two drugs
- Insufficient information was included in detail aid to allow informed decision of true comparison between treatments
- In a commentary on the REAL study, Ferrari and Rizzoli stated “this observational study (REAL) by design cannot demonstrate whether there are real differences in efficacy between the two drugs. However it might suggest that to reproduce drug efficacy, as demonstrated in RCTs, in real life, full adherence to treatment is required.”

In closing comments, the sanofi-aventis representatives made the following points:

- The detail aid highlights differences with respect to early fracture risk reduction, at 6 months and twelve months. It does not claim overall superior efficacy of Actonel.
- There are agreed limitations of observational studies; the detail aid seeks to communicate the trends shown by the body evidence.

The MSDA and sanofi-aventis representatives left the meeting following these presentations.

Appeals Committee members considered the referenced data for both alendronate and risedronate and were of the view that both were effective treatments for osteoporosis however there was no data that supported the view that one treatment was more effective overall than the other. The Committee noted sanofi-aventis’ argument that the detail aid should be considered in the context of claims about early reduction of fracture risk with Actonel. It was noted that

whilst there is evidence that risedronate reduces the risk of non-vertebral fractures after six months’ treatment in an appropriately selected group of patients, there is currently no evidence that this is also the case for alendronate.

The Committee was of the view that although not every page of the detail aid made a direct comparison between alendronate and risedronate, the overall inference was there; the inclusion of the data for a competitor product invites the comparison between the two products. It was also noted that the headings on each page added to the comparative nature of the piece. Direct comparisons between alendronate and risedronate were made on three pages of the detail aid.

The Appeals Committee considered each aspect of the sanofi-aventis appeal.

Item 3.1 in complaint - Graphs representing non vertebral fracture data for Alendronate and Actonel

The Appeals Committee accepted that the graphs pertaining to non-vertebral fracture data for alendronate and risedronate were on separate pages and were annotated with either alendronate vs placebo and risedronate vs placebo. There was a brief description of the relevant studies and references, which should not lead a healthcare professional to the view that the graphs represented a head to head comparison. On this point the Appeals Committee differed from the Code Committee. However the Appeals Committee remained of the view that the presentation of the data on alendronate and linking the information with that for risedronate through headings and claims was clearly intended to invite comparison, which in this case was misleading. The referenced studies were different patient populations and trial designs; it was not clear to a reader that in the alendronate study patients were initiated on a low dose of 5mg and switched to 10mg after two years. It was further noted there was a trend in the meta-analysis to reflect a greater effect with higher dosing of alendronate. The inferred comparison between alendronate and Actonel was therefore not fair and was misleading. The Appeals

Committee did not uphold the appeal in relation to the breach of Section 1.3 of the Code.

Item 3.5 in the complaint - "Actonel reduces the risk of hip fracture by 60% in women with established osteoporosis"

The Appeals Committee did not uphold the appeal in relation to the breach of Section 1.3 of the Code for the reasons set out by the Code of Conduct Committee. The Appeals Committee noted that sanofi-aventis had agreed to amend and clarify this claim.

Item 3.8 in the complaint - REAL study - quote, claims and statements based on the results of the REAL Study

The Appeals Committee accepted that the REAL study was appropriately conducted. Nevertheless the two patient populations - those treated with alendronate and those with risedronate - were not directly comparable at baseline, which is a limitation of the study data. This limitation would not be apparent to a reader and had not been clearly communicated in the detail aid. The Appeals Committee did not uphold the appeal in relation to the breach of Sections 1.2.2 and 1.3 of the Code for the reasons set out by the Code of Conduct Committee.

Sanctions

Having not upheld the appeal, the Appeals Committee considered whether the sanctions determined by the Code of Conduct Committee were appropriate. The Committee considered that this was a moderate breach of the Code that was likely to have an effect on how the medical profession would prescribe the product.

The Committee determined that sanofi-aventis should:

- Withdraw the Detail Aid found in breach and allow no further appearance of the graphs and claims found in breach of the Code in the same or similar form.
- Send a Corrective letter to all General Practitioners who had been detailed with the item found in breach of the Code, informing them that at present there are inadequate data to differentiate between risedronate and alendronate. The content of this corrective letter must be

approved by the Committee prior to distribution.

- Pay a fine of \$80,000. The Appeals Committee reduced the fine, which was at the upper limit of fines although the breach was considered moderate, after consideration of sanctions applied to breaches of a similar nature.

Femara 878

Complainant: AstraZeneca

Subject Company: Novartis Pharmaceuticals

Product: Femara

Complaint

AstraZeneca alleged that Novartis' promotion of Femara used only a 26-month analysis of the BIG 1-98 study when a 51-month analysis had also been published, resulting in inaccurate promotional items due to the omission of information reflecting the most current data available.

The second aspect of the complaint related to the outcome measure Time to Distant Recurrence (TTDR) which is identified as an exploratory endpoint in the BIG 1-98 publication, whereas in the Femara Product Information the endpoint is stated as Distant Disease Free Survival (DDFS) and described as a secondary endpoint of the trial.

Sections of the Code

Materials alleged to be in breach of the following Sections of the Code:

- 1.2.2 Level of Substantiating Data
- 1.3 False and Misleading Claims

Response

Novartis had responded that they believe that the Primary Code Analysis of the BIG 1-98 trial is the first and only complete analysis and remains the reference data set for promotional items for letrozole (Femara).

In relation to the terminology for the endpoint, Novartis was of the view that whether it is defined as "additional" or "secondary" is immaterial when they have undergone regulatory scrutiny and are accepted by the clinical community as being highly relevant.

Code of Conduct Decision

Issue 1: Continued promotion of the Breast International Group (BIG) 1-98 26-month analysis without any reference to the 51-month analysis

No breach of Section 1.3 of the Code

Issue 2: Use of Time to Distant Recurrence

No breach of Section 1.2.2 of the Code

Consideration of the Complaint

The Committee noted the extensive negotiation and dialogue between AstraZeneca and Novartis and that there had been a similar complaint considered in New Zealand.

The Committee reviewed the Breast Cancer International Group (BIG) 1-98 Study first publication and subsequent analysis. The study is a randomised, phase 3, double blind trial that compared five years of treatment with various adjuvant endocrine therapy regimens in post menopausal women with hormone receptor-positive breast cancer. Subjects were randomised to receive either:

- Letrozole
- Letrozole followed by tamoxifen
- Tamoxifen
- Tamoxifen followed by letrozole

Two analyses of the BIG 1-98 study have been published:

New England Journal of Medicine (NEJM), 29 December, 2005

- This analysis, referred to as the Primary Core Analysis, compared the two groups assigned to receive letrozole alone (letrozole alone and letrozole prior to switching to tamoxifen) with the two groups assigned to receive tamoxifen alone (tamoxifen alone and tamoxifen prior to switching to letrozole) for the first two years of the study.
- Outcomes for subjects in the two sequential-treatment groups were included up to the time that treatments were switched at two years.

Journal of Clinical Oncology (JCO), 2 January 2007

This second analysis of the data included only those subjects in the letrozole-only and tamoxifen-only arms of the study, i.e. excluding the two arms where subjects would switch to the alternative treatment. The authors stated that they had conducted this analysis to assist other investigators who may wish to perform meta-analyses of these data. The authors had also stated that the primary analysis published in the NEJM may unduly over-represent early events. The second published analysis was limited to patients randomly assigned to continuous therapy arms, so the number of subjects

included in this analysis was lower than the total group in the trial, and included protocol-defined updated results. The second analysis had not been submitted to the FDA or TGA because Novartis did not have access to these data and was therefore not included in the Femara Product Information.

The Committee noted that the Primary Core Analysis was the basis on which letrozole was registered in Australia. It was also noted that further analyses had been planned by the study investigators. The JCO analysis at 51-months was one of the additional analyses. In considering the complaint Members commented that the results from the JCO analysis were supportive of the primary core analysis.

Issue 1: Continued promotion of the Breast International Group (BIG) 1-98 26-month analysis without any reference to the 51-month analysis

Members commented that the issue to be considered is whether the 51-month data is materially or substantially different to the primary core analysis which could potentially make the Femara promotional materials misleading. The Committee was of the view that the use of the primary core analysis as substantiating data for the promotional items was not misleading as the 2007 JCO analysis was essentially confirmatory of the primary core analysis and because the claims were supported by the Product Information. The NEJM analysis was a primary core analysis performed in accordance with the protocol.

The Committee did not agree with AstraZeneca's assertion that the JCO analysis was a further interim analysis, following the analyses performed by the Data Safety Monitoring Board, described in the protocol, when 24% of events and 67% of events had been accrued. The JCO was an additional analysis documented as a late protocol amendment, for the reasons stated by the investigators noted above. The JCO published analysis is not materially or substantially different to the primary analysis published in the NEJM.

The Committee unanimously found no breach of Section 1.3 of the Code.

Members commented that it takes a long time to collect and analyse data in breast cancer trials, however accrued evidence can be reported in real time. Some members suggested that it may be useful in the future to include an explanatory statement with the BIG 1-98 results that these results are definitive in real time but further analyses have been planned and will resolve the potential early event bias identified by the investigators.

Issue 2: Use of Time to Distant Recurrence (TTDR)

The Committee noted AstraZeneca's statement that in the BIG 1-98 publications TTDR is listed as an exploratory endpoint, however in the Femara Product Information it is identified as Distant Disease Free Survival (DDFS) and a secondary endpoint.

The Committee noted that AstraZeneca and Novartis agreed on the importance and clinical validity of distant cancer recurrence which indicates a worse prognosis than local recurrence of breast cancer. Members also noted that Novartis was currently seeking clarification from the IBCSG on this matter.

The Committee noted that the measure of TTDR was not included in the original study protocol but was added to the statistical analysis plan as being an important emerging measure for the future.

Members noted that the TGA had accepted the term DDFS, which is essentially the same as TTDR and reflected the same statistical data published in the results. There was very little difference between TTDR and DDFS and DDFS had been accepted by TGA. Novartis should be able to use this endpoint in its promotional material. However members were also aware that there had been discussion within the FDA that the use of DDFS is not specific to breast cancer as there could be other causes of death in the breast cancer study patients.

Members considered that AstraZeneca's arguments concerning whether this was an exploratory or secondary endpoint were not sustainable. This is an endpoint that emerged as relevant during the study, and the analysis was done carefully and properly

and described in the change to the statistical analysis. One member suggested that if future advertisements refer to risk of distant recurrence that it might assist interpretation of the data by also presenting the primary outcome measure in all advertisements, and making it clear that the DDFS is a measure of events not a time measure.

The Committee unanimously found no breach of Section 1.2.2 of the Code in relation to use of the DDFS endpoint in the Femara promotional material.

Seretide 879

Subject Company: GlaxoSmithKline
Australia (GSKA)

Complainants: Boehringer Ingelheim &
Pfizer Australia

Product: Seretide

Complaint

The complainants alleged that GSKA had not provided adequate references to substantiate the claim “*Add Seretide COPD to slow disease progression*” (COPD is chronic obstructive pulmonary disease) and that the claims in relation to the PBS listing for Seretide for COPD were misleading.

Sections of the Code

Materials alleged to be in breach of the following Section of the Code:

- 1.2.2 Level of Substantiating Data
- 1.3 False and Misleading Claims
- Preamble to Section 3, Promotional Material
- 3.1.1.3 Primary Advertisement

Response

GSKA stated that it had relied on an appropriate body of evidence and correctly represented the data from the relevant peer-reviewed publications. In relation to the PBS listing claim, GSKA stated that a reader would be sufficiently alerted to the restricted benefit listing for Seretide.

Code of Conduct Decision

Add Seretide COPD to slow disease progression

By a unanimous decision the Committee found no breach of Sections 1.2.2 or 1.3 of the Code

“We are now PBS listed for COPD” and “Seretide is now listed for COPD”

By a majority decision the Committee found a breach of Section 1.3 of the Code.

By a unanimous decision the Committee found no breach of the preamble to Section 3 of the Code.

No PBS information on the advertisement flap

By a unanimous decision the Committee found a breach of the preamble to Section 3 and Section 3.1.1.3 of the Code.

Sanction

Withdraw material found in breach

Pay a fine of \$50,000

Consideration of the Complaint

The Committee considered the chronology of events and key issues in relation to this complaint:

Jones & Agusti 2006

- Questions the reliability of 1977 study on change in FEV₁ (forced expiratory volume in one second) as the sole measure of COPD progression
- Offers a list of several indices and recommends use of several measures of disease progression rather than one

TORCH Study published in February 2007 in the New England Journal of Medicine (NEJM)

- Three year study in COPD of all cause mortality
- Included a number of measures including:
 - Quality of Life (QoL): St George's Respiratory Questionnaire (SGRQ)
 - Number of exacerbations
 - FEV₁

Letters to the Editor of the NEJM after the publication of TORCH, 24 May 2007

- P J Barnes: rate of decline in FEV₁ not significant
- P Calverley, the primary author of the TORCH study, responded: rate of decline in lung function could not be inferred from the spirometric data in the TORCH study

Data on rate of decline

- Abstract of the analysis of the TORCH data presented at American Thoracic Society (ATS) May 2007
- Poster of the analysis of the TORCH data presented at European Respiratory Society (ERS)
- Further analysis of the TORCH data has been completed and presented at ERS, which showed that the rate of decline in FEV₁ does change with the

salmeterol/fluticasone propionate combination - this now supersedes the previous statements on the rate of decline.

27 July 2007 advertisement subject to complaint published

3 August 2007 complaint from Boehringer Ingelheim & Pfizer sent to GSK

17 August 2007 GSK wrote to Boehringer Ingelheim/Pfizer with a proposal about including a combination of indices in the Seretide COPD advertisements

- Improvements in QoL
- improvement in exacerbations
- Improvements in "lung function over time"
- Reduction in inflammation

27 August 2007 teleconference between Boehringer Ingelheim, Pfizer and GSKA

- Agreement achieved on indices of disease progression
- Disagreed that there is sufficient evidence (rate of declines in FEV₁)

17 September 2007 complaint submitted to MA

Indices of positive impact on COPD progression available for Seretide from TORCH study

- Exacerbations: statistically significant
- QoL: statistically significant
- FEV₁: statistically significant at end of study (rate not included in first publication - subsequently shown to be statistically significant)
- Indices of inflammation (Barnes 2006)

Complaint 1: "Add Seretide COPD to slow disease progression"

Members were of the view that having reviewed the studies provided by the parties to the complaint, there is evidence to support the concept that more than one marker should be taken into account when considering the "rate of disease progression" in COPD. Members stated that collectively the references supported the claim.

While agreeing that the broad scope and measures of outcomes were valid in disease progression and QoL some members were of the view that there could be more

qualification and explanation within the body of the advertisement and more comprehensive referencing. The Committee noted that the references to support the claim listed in the advertisement were the Seretide Product Information, the TORCH study (Calverley et al NEJM) and Barnes (2006). The further analysis of the TORCH data presented at the ERS was not included as a reference. However, the TORCH study did demonstrate statistical improvements in FEV₁, exacerbation rates and QoL measures. In a unanimous decision the Committee found no breach of Sections 1.2.2 and 1.3 of the Code

"We are now PBS listed for COPD" and "Seretide is now listed for COPD"

Members were of the view that while the mandatory PBS box appeared on the second page of the advertisement, the statements "We are now PBS listed for COPD" and "Seretide is now listed for COPD" in large font on the front page gave the impression that Seretide was PBS listed for all COPD patients, without qualification. Members commented that while it may be reasonable to expect a reader to turn the page, it was misleading to not have qualified or referenced the very large and bold statements to ensure a reader would be directed to a statement on the same page which advised that the restricted PBS benefit was for a discrete subgroup of COPD patients.

In a majority decision the Committee found a breach of Section 1.3 of the Code and in a unanimous decision the Committee found no breach of the preamble to Section 3 of the Code.

No PBS information of the advertisement flap

Having reviewed the advertisement subject to complaint in the form it appeared (*Australian Doctor* 27 July - first page inserted after page 8 with flap after page 56) members determined that the item should be treated as two advertisements, the first comprising the two full-sized pages appearing after page 8 and the second comprising the 'flap' page appearing after page 56. The Committee noted that GSKA had not been able to provide any evidence that it had requested *Australian Doctor* to publish the advertisement as a centerfold.

The Committee commented that a company should be able to provide evidence of instructions for publications, for example the date of publication and positioning in the publication.

The Committee considered that the information on the flap advertisement should have complied with all requirements for an advertisement, including the PBS information, as it was separate from the other advertisement which contained the mandatory PBS information.

In a unanimous decision the Committee found a breach of the preamble to Section 3 and Section 1.3 of the Code.

Sanction

Having found several breaches of the Code, the Committee considered an appropriate sanction. The Committee considered that this constituted a moderate breach of the Code. Whilst there was no suggestion of major patient safety issues, the use of a broad statement pertaining to PBS reimbursement for COPD without adequate qualification may influence prescribers in their choice of product for those patients whose COPD is less likely to benefit.

The Committee determined that GSKA should:

- Take immediate action to cease using the advertisements found in breach of the Code and not use them again in the same or similar form unless they fully comply with the Code
- Pay a fine of \$50,000

The Committee considered and determined that there was no requirement for corrective action.

Appeal Committee

An appeal was lodged by the complainants BI and Pfizer against the decision of the Code Committee to find no breach in relation to the claim "*Add Seretide COPD to slow disease progression*". BI and Pfizer stated that their complaint had insufficiently emphasized the importance and significance to the market of this claim and had inadequately described the appropriate context in which to assess the claim and this may have contributed to the Committee

arriving at, what the companies believe is, an incorrect decision. BI and Pfizer believe that to substantiate the claim 'slows disease progression' GSK must provide evidence that Seretide slows deterioration in the lung function measure FEV1 (Forced Expiratory Volume in one second)

GSKA response to the appeal

GSKA stated that BI/Pfizer had had ample opportunity to present the context and emphasis in their argument to GSKA in intercompany dialogue and the Code of Conduct Committee. GSKA also maintained that BI/Pfizer had not provided any new information or demonstrated an error in the Code of Conduct Committee's process to warrant this appeal. GSKA stated that the promotional material and claims were consistent with current local and international evidence-based COPD treatment guidelines.

Appeals Committee Determination

In a unanimous decision the Committee determined not to uphold the appeal by BI and Pfizer in relation to the finding of no breach of 1.2.2 or 1.3 of the Code with respect to the claim "*Add Seretide COPD to slow disease progression*".

Consideration of the Appeal

The following summarises the BI appeal as presented:

- BI and Pfizer consider that the Code Committee erred in not adequately considering the magnitude of the claim "*Add Seretide COPD to slow disease progression*", which is a significant and new claim with respect to COPD and is not supported by evidence or the Product Information (PI).
- COPD indication for Seretide is "For the symptomatic treatment of patients with severe COPD (FEV1<50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular beta 2 agonist bronchodilator therapy."
- The claim is in breach of Section 1.2.2 because there is no unequivocal or highest level of evidence to support the claim and therefore the claim is also false and misleading and in breach of Section 1.3.

- The PI includes no indication for “slowing of disease progression”; the COPD indication is only for symptomatic treatment.
 - The TORCH study is a very big and important long term COPD study
 - Primary outcome was difference in all cause mortality for the comparison between the combination regimen and placebo (which did not achieve conventional levels of statistical significance)
 - Secondary outcomes
 - ❖ frequency of COPD exacerbations
 - ❖ Health status according to St George’s Respiratory questionnaire
 - Other outcomes
 - ❖ COPD related mortality
 - ❖ ‘On treatment’ mortality
 - ❖ Severe COPD exacerbations
 - ❖ Clinic post-bronchodilator FEV1 (which is not equivalent to rate of decline in FEV1)
 - TORCH does not address “disease progression” - focus was on mortality
 - Statistical analysis of TORCH does not support the claim that the treatment reduces mortality
 - In relation to the other reference for the claim, Barnes et al (*American Journal of Respiratory and Critical Care Medicine*, 2006):
 - It was “a proof-of-principle study to ascertain whether inhaled therapy can modify inflammation in COPD”
 - Methodology included bronchial biopsies and induced sputum from 140 subjects
 - Conclusion: The combination of salmeterol and fluticasone propionate has a broad spectrum of anti-inflammatory effects in both current and former smokers with COPD
 - It does not address COPD disease progression and does not support the claim
 - In making the claim that Seretide slows disease progression, GSK is in breach of:
 - Code Section 1.2.2 Level of substantiating data as none of the references (the Seretide PI, Calverley 2007, Barnes 2006) address disease progression
 - Code Section 1.3 False or misleading claims
 - ❖ current Australian and global evidence-based COPD treatment guidelines - only smoking cessation has been shown to slow disease progression
 - ❖ under current regulatory guidelines, trials specifically designed to investigate rate of decline in FEV1 are needed to claim slowing of disease progression
- The following is a summary of the expert evidence presented:
- A graph was referenced from an article by Fletcher and Peto in the *British Medical Journal*, June 1977 describing the natural decline in lung function measured by FEV1
 - The ‘Holy Grail’ of COPD Research is to modify the rate of decline of lung function as measured by FEV1. Whilst there have been multiple randomised clinical trials attempting to prove an intervention changes the rate of decline, these have only been able to shift the curve to the right (indicating delayed onset of decline) but the rate of decline remains unaffected.
 - The results of various trials were discussed:
 - Effects of Budesonide on mild COPD - rate of decline the same
 - ISOLDE Trial in more severe COPD - no difference in rate of decline
 - Pooled Analysis of seven studies on FEV1 rate of decline - no difference
 - TORCH Study
 - There is no analysis in the published study of the rate of decline in FEV1
 - The further data analysis of post-bronchodilator FEV1 showed the rate of decline was significantly different with Seretide but is only in abstract, has not received peer review or been published
 - This result is at variance with other studies
 - The methodology behind the further analysis was not described in the TORCH publication

- Quality control of spirometry such as calibration of instruments, performance of test, has not been described or published; this is particularly important because the study was of 6112 patients in 444 centres in 42 countries
- Is the FEV1 the appropriate measure of disease progression?
 - Conventionally and universally accepted as the measure of progression
 - Jones and Augusti (2006) suggest rate of decline of FEV1 or health status but the rate of decline in health status is known to be less with fluticasone since ISOLDE study (2000), yet there has been no change to the guidelines that state that only smoking cessation is effective in changing the rate of decline in lung function
 - Patient centred outcomes (TDI, exercise capacity, health status) are accepted as measures of treatment effect but not of disease progression.
- The published TORCH study does not support a claim for the study medications to slow progression of COPD
- There are a number of abstracts with data to demonstrate an effect of drugs on disease progression but these need to be peer reviewed before they can lead to the claim that the Holy Grail has been found.

The following summarises the GSKA response to the appeal:

- GSKA do not agree that an error in the Code Committee's process or outcome has occurred
 - BI/Pfizer has had ample opportunity to present their case in the original complaint.
 - GSKA does not believe that the complainant placing *"insufficient emphasis"* on the claim and *"inadequately describing the appropriate context"* equates to altering medical validity of data presented
 - No new information has been provided by BI/Pfizer
 - The Code Committee Members unanimously found the claim not in breach
- There is evidence to support the concept that more than one marker should be taken into account when considering the "rate of disease progression" in COPD.
 - Members of the Code of Conduct Committee stated that collectively the references supported the claim.
 - BI/Pfizer maintain that rate of decline in FEV1 is the only relevant measure of COPD disease progression
 - GSK's claim is consistent with local and international, evidence-based treatment guidelines
 - GOLD
 - COPD-X (Australasian)
 - International guidelines recognise the need for multiple disease indices including:
 - Inflammation
 - Exacerbations
 - Quality of life
 - Lung Function
 - International GOLD guidelines support the use of multiple disease markers as indicators of disease progression:
 - *"Patients with COPD are heterogeneous in terms of their clinical presentation, co-morbidities, underlying lung pathology, disease severity, and rate of disease progression. Thus it is highly unlikely that a single measure can accurately assess the severity of COPD, predict patient prognosis, and evaluate the effectiveness of therapy, thereby measuring all dimensions of the disease."*
 - *"Since inflammation is a feature of COPD, it follows that anti-inflammatory therapies may have clinical benefit in controlling symptoms, preventing exacerbations, and slowing the progression of the disease" (GOLD Guidelines 2005)*
 - Jones and Agusti recognised the need for multiple markers of disease progression: *"The concept of a single global marker has the attraction of simplicity and convenience but may not be appropriate to a complex, multi-component disorder such as COPD" (Jones & Agusti 2005).*
 - The 2007 GOLD Guidelines recognise several markers of disease progression *"...neither bronchodilator nor oral*

glucocorticosteroid reversibility testing predicts disease progression, whether judged by decline in FEV1, deterioration of health status, or frequency of exacerbations.....”(GOLD Guidelines 2007)

- BI/Pfizer had questioned the validity of the TORCH study as supporting evidence for changing the rate of decline in lung function and questioned the methodology for assessing FEV1 in TORCH
- TORCH is the largest and most comprehensive study of COPD. It compared combination therapy and monotherapy with long acting beta agonist and inhaled corticosteroids versus placebo. TORCH showed statistically significant advantages for Seretide in health status, frequency of exacerbations, use of oral steroids, and - probably most importantly clinically - protection against a decline in lung function. Change in rate of decline in FEV1 can be obtained from the TORCH data; the quality control on spirometry was adequate.
- The further analysis of TORCH for FEV1 rate of decline is being peer reviewed for publication.
- There is a body of evidence that supports having more than one marker of COPD disease progression
- GSK maintained their original position regarding this claim - that it is supported by the body of evidence including local and international guidelines.

Following questions in relation to the spirometry measurements in the TORCH study, it was stated that there were 26,000 spirometric observations available for the analysis. Spirometers were calibrated according to the manufacturers' recommendations and a calibration log was kept. Lung function data were reviewed centrally during the study and queried if values differed significantly in consecutive visits. The standard deviation of the FEV1 measurements was comparable to that of previous studies where spirometry was performed using more vigorous quality control. With 26,000 observations any error would be balanced out.

A Member of the Appeals Committee questioned the BI representatives concerning their interpretation of the primary outcome in the TORCH study (all-cause mortality), which very nearly reached statistical significance at a p-value of 0.052. The response was that TORCH probably did show a real change in mortality rate despite not achieving conventional levels of statistical significance, but that in his opinion this is not the same as disease progression. An opinion was put forward that it is appropriate to measure treatment effects from a patient-centred perspective, recognising that these effects do not always correlate well with changes in FEV1. However, in his opinion the measure of disease progression in COPD is universally regarded to be measured by change in FEV1.

The Boehringer Ingelheim and GSKA representatives left the meeting following these presentations.

The Committee considered the primary audience for this item, which was published in *Australian Doctor*, how would a general practitioner view the claim “slows disease progression”, and how the interpretation of such a claim might impact prescribing of the product. Members considered that the academic or clinical researcher's view of “slows disease progression” may differ from that of a general practitioner, and also from that of a specialist respiratory physician. Healthcare professional members of the Committee took the view that “slows disease progression” could mean, to the target audience, delaying the onset of worsening of a disease or death, rather than necessarily a slowing of the rate of decline of an organ's function. Some members also commented that if an individual patient's FEV1 measurement remained at the same level but the patient reported fewer exacerbations, an increase in normal activity levels and better ability to perform day to day tasks, improved sleep, or less breathlessness they would consider these effects to indicate ‘delayed’ or ‘slowed’ disease progression. Members considered that a GP would be unlikely to rely solely on FEV1 measurements as the indicator of COPD disease progression.

Members discussed the additional analysis of change in FEV1 from the TORCH data, which has not been published in a peer reviewed journal. It was noted that an abstract may not be used as the sole supporting evidence for a claim but can be used as a secondary reference to support other evidence. The abstract of the additional analysis of decline in FEV1 had not been referenced in the advertisement. Members expressed caution about reliance on the unpublished additional analysis to support the claim if FEV1 was the only measure of disease progression.

Members were of the view that, on balance, there is sufficient evidence taken in its entirety to support the notion that more than one marker could be taken into account when considering the “rate of disease progression” in COPD, not just change in FEV1. In considering the published TORCH study as an example, some members of the Appeals Committee expressed their concern in principle about companies making promotional claims based on analyses of secondary endpoints from a study for which the primary endpoint did not reach conventional levels of statistical significance. In this particular case, however, Members agreed with the Code of Conduct Committee that the claim in question was also supported by the broad balance of evidence, including the Barnes et al study, for which the primary endpoint was reduction in inflammation, the TORCH study secondary endpoints and the Seretide Product Information.

Members considered that the claim was not inconsistent with the Product Information, although Seretide is not specifically indicated for slowing COPD disease progression.

The Appeals Committee agreed with the decision and reasoning by the Code of Conduct Committee that collectively the cited references supported the claim:

“While agreeing that the broad scope and measures of outcomes were valid in disease progression and QoL some members were of the view that there could be more qualification and explanation within the body of the advertisement and more comprehensive referencing. The Committee

noted that the references to support the claim listed in the advertisement were the Seretide Product Information, the TORCH study (Calverley et al NEJM) and Barnes (2006). The further analysis of the TORCH data presented at the ERS was not included as a reference. However, the TORCH study did demonstrate statistical improvements in FEV1, exacerbation rates and QoL measures. In a unanimous decision the Committee found no breach of Sections 1.2.2 and 1.3 of the Code.”

The Committee also considered that many COPD Guidelines take a broader view of disease progression than only considering FEV1. Further, the claim would be read in the context of the statement above the claim - *“reducing inflammation decreases exacerbations and helps to slow disease progression”*.

The Appeals Committee did not uphold the appeal and as such the claim “slows disease progression” was determined to be not in breach of Sections 1.2.2 and 1.3 of the Code.

The Appeals Committee strongly recommended that GSKA should immediately implement inclusion of the qualifying statement with the disease progression claim that was offered during intercompany dialogue and review the referencing used to support the claim, as recommended by the Code Committee.

Famvir 880

Subject Company: Novartis Pharmaceuticals

Complainant: Healthcare Professional

Product: Famvir

Complaint

The complainant alleged that that a brochure for Famvir was misleading as it ignored symptomatic treatment as a reasonable option for cold sores and it ignored low level near infra red light treatment as a scientifically tested, effective and safer approach to the treatment of herpes labialis.

Sections of the Code

Materials alleged to be in breach of the following Sections of the Code:

- 1.1 Responsibility
- 1.2 Substantiating Data
- 1.3 False and Misleading Claims

Response

Novartis stated that the content of the promotional material for Famvir was balanced, accurate, correct, not misleading and fully supported by the product information, current published literature and the current treatment guidelines. Novartis also noted that low level near infra red light therapy has not been approved by the TGA for the treatment of cold sores.

Claim 1: "... until now sufferers have only had topical anti-viral creams from their pharmacist to rely on..."

- It ignores symptomatic treatment as a reasonable approach to, in most cases, a relatively benign condition
- It ignores low level near infra red light therapy as a scientifically tested effective, available and arguably safer approach to treatment of herpes labialis

Committee decision

In a unanimous decision the Committee found no breach of Sections 1.1, 1.2 or 1.3 of the Code.

Consideration of the complaint

Members noted that Herpes labialis or cold sores are caused by herpes simplex virus type 1 (HSV-1) and whilst a cold sore may be considered 'simple', HSV infection is not

a benign illness and is highly contagious and can lead to serious illness.

Famvir is indicated for the treatment of recurrent herpes labialis (cold sores) in immunocompetent adult patients. It is also indicated in immunocompromised patients for the treatment and suppression of recurrent herpes simplex. Members noted that the Product Information for Famvir and the clinical evidence supported the use of Famvir for the treatment of herpes labialis. However some members were of the view that the statement "*until now sufferers have only had topical anti-viral creams from their pharmacist to rely on*" could have better communicated that the reference was only to approved pharmacologic treatments.

In relation to the assertion by the complainant that Novartis had ignored the use of low level near infra red (NIR) light therapy, the Committee noted that this treatment has not been approved by the Therapeutic Goods Administration (TGA) for the treatment of cold sores. Members were also of the view that little evidence had been presented to demonstrate the safety and efficacy of NIR light therapy. The reference cited by the complainant was a small study that just reached statistical significance. Further, there was doubt expressed regarding the general availability of this therapy to general practitioners.

By a unanimous decision, the Committee found no breach of Sections 1.1, 1.2 or 1.3 of the Code for the reasons outlined above.