



## Specialist Medical Review Council

### Declaration and Statement of Reasons

*Section 196W*

*Veterans' Entitlements Act 1986*

**Re: The decision by the Repatriation Medical Authority not to amend the Statements of Principles 96 and 97 of 2014 in respect of malignant neoplasm of the breast**

1. In relation to the Repatriation Medical Authority (the Authority) Statements of Principles **Nos. 96 and 97 of 2014 concerning malignant neoplasm of the breast (as amended)** made under subsection 196B of the *Veterans' Entitlements Act 1986* (the Act), the Council:

DECLARES, under subsection 196W(5)(b) of the Act, that there is insufficient sound medical-scientific evidence on which the Authority could have relied to amend the Statements of Principles with respect to non-oral combined hormonal contraceptives; and

RECOMMENDS that the Authority undertake a further review of the Statements of Principles having regard to replacing the defined term of 'combined oral contraceptive pill' with the defined term of 'combined hormonal contraceptive' where it appears in clause 6(c), 6(c)(i) and 6(c)(ii), which, in the opinion of the Council, reflects the classification of contraceptives used in current medical practice.

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## EXECUTIVE SUMMARY

1. The following document outlines the Reasons for Decisions (the Reasons) for the declaration and recommendation made by the Specialist Medical Review Council (SMRC) in relation to the Repatriation Medical Authority (the RMA) Statements of Principles for Nos. 96 and 97 concerning malignant neoplasm of the breast (as amended), made under subsection 196B of the *Veterans' Entitlements Act 1986* (the VEA). The SMRC is an independent statutory body established by the VEA. Upon receipt of a valid application, a Review Council (the Council) is formed under section 196ZK of the VEA. The SMRC received a valid application seeking a review of Statements of Principles for Nos. 96 and 97 in respect of taking combined hormonal contraceptives as a factor for malignant neoplasm of the breast. In conducting a review, the Council must review all the information that was available to the RMA when it made and reviewed the Statements of Principles Nos. 96 and 97 and determine whether or not there is sound medical-scientific evidence as defined by section 5AB(2) of the VEA that indicates a 'relevant association' connecting the particular injury, disease or death to the relevant service set out in Section 196B(2) and 196B(3) of the VEA.
2. In defining the scope of the review, the Council decided that it would have particular regard to whether there was sound medical-scientific evidence on which the RMA could have relied to amend either or both of the Statements of Principles Nos. 96 and 97 in any or all of the following ways:
  - (1) whether there was sufficient sound medical-scientific evidence before the RMA on which to amend the Statements of Principles to include the use of non-oral forms of combined hormonal contraceptives in relation to malignant neoplasm of the breast; and
  - (2) if so, to determine relevant factors for inclusion in those Statements of Principles.

3. In forming its decisions on the sound medical-scientific evidence, the Council brought to bear its scientific expertise and judgement and applied criteria and tools to be taken into account by epidemiologists as applicable for determining causation.
4. The Reasons presents two principal findings from the Council's review. First, in relation to determining whether there was sufficient sound medical-scientific evidence before the RMA on which to amend the Statements of Principles Nos. 96 and 97 concerning malignant neoplasm of the breast to include the use of non-oral combined hormonal contraceptives as a factor, no relevant association was found. The Council's review of the sound medical-scientific evidence identified neither risk nor protection from non-oral combined hormonal contraceptives in relation to malignant neoplasm of the breast. Second, in relation to determining relevant factors for inclusion in the Statements of Principles Nos. 96 and 97 concerning malignant neoplasm of the breast, a finding is reported without the possibility of assessing for a relevant association: from this, a recommendation for the RMA to undertake a further review having regard to re-classification of contraceptives is made.
5. The Council concluded that there should not be an amendment to the Statement of Principles concerning non-oral combined hormonal contraceptives in relation to the Statements of Principles Nos. 96 and 97 concerning malignant neoplasm of the breast. This conclusion was based on insufficient evidence available to satisfy the requirements of a relevant association. Rather, the Council recommends the RMA undertake a further review of the Statement of Principles having regard to incorporating a category comprising of combined hormonal contraceptives by replacing the term 'combined oral contraceptive pill' with 'combined hormonal contraceptives'. The Council formed a view that the classification of contraceptives as relevant to the possible causation of malignant neoplasm of the breast that appears in the Statements of Principles Nos. 96 and 97 does not reflect the current classification of contraceptives in medical practice.

6. The Council formed a view that while it is not currently possible to determine a relevant association for non-oral combined hormonal contraceptives and malignant neoplasm of the breast, a further review of the epidemiological study of relationships between contraceptives and a variety of health outcomes may produce different results if the classification of contraceptives were to reflect current medical practice. In forming this view, the Council started from the position that there is already an established causal relationship between the combined oral contraceptive pill and malignant neoplasm of the breast, as established by the Statements of Principles Nos. 96 and 97. It also took into account sound medical-scientific evidence that considers non-oral combined hormonal contraceptives to be of the same class as the combined oral contraceptive pill and that despite not identifying an association with malignant neoplasm of the breast, cases were reported by the only study that has investigated non-oral combined hormonal contraceptives and malignant neoplasm of the breast.

# REASONS FOR DECISIONS

## INTRODUCTION

1. In relation to the Repatriation Medical Authority (the RMA) Statements of Principles for Nos. 96 and 97 concerning malignant neoplasm of the breast (as amended), made under subsection 196B of the *Veterans' Entitlements Act 1986* (the VEA), this document outlines the Reasons for Decisions (the Reasons) for the declaration and recommendation made by the Specialist Medical Review Council (SMRC) for these Statements of Principles to be amended. This section of the Reasons will introduce the role of the SMRC, the events that led to a review of these Statements of Principles by the SMRC, and the types of information and how they were considered in this review.
2. The Specialist Medical Review Council (SMRC) is an independent statutory body established by the VEA. In general terms, upon receipt of a valid application, a Review Council (the Council) is formed under section 196ZK of the VEA to review as relevant:
  - a decision of the RMA regarding the contents of Statements of Principles in respect of a particular kind of injury, disease or death; or
  - a decision of the RMA not to determine, not to amend, Statements of Principles in respect of a particular kind of injury, disease or death.
3. On 29 November 2020, the RMA received an application to investigate the contents of Statements of Principles in respect of taking combined hormonal contraceptives as a factor for malignant neoplasm of the breast (Instruments Nos. 96 and 97 of 2014, as amended). The Applicant was a person eligible to make a claim for compensation under section 319 of the *Military Rehabilitation and Compensation Act 2004* (MRCA).
4. On 16 February 2021, the RMA decided to conduct the review to determine whether there was sufficient sound medical-scientific evidence to justify an amendment to these Statements of Principles in accordance with the Applicant's request.

5. On 7 April 2021, the RMA decided that the new sound medical-scientific evidence provided by the Applicant, together with the sound medical-scientific evidence it had previously considered, was not sufficient to justify the amendments sought by the Applicant. When the RMA informed the Applicant of the decision, the RMA did not inform the Applicant of the right to have the decision reviewed by the SMRC (including the relevant time limit) under section 196Y(2)(b)<sup>1</sup> of the VEA.
6. On 4 August 2021, the Applicant lodged a request to the SMRC seeking a review of the RMA's 7 April 2021 decision. As the application was lodged outside the three-month timeframe required by 196Y(2)(b) of the VEA, there was no discretion for the SMRC to undertake the review. The SMRC drew this issue to the attention of the RMA, noting the Applicant had not been informed of the right of an SMRC review.
7. On 22 October 2021, the RMA remade the 23 April 2021 declaration to allow the Applicant to seek an SMRC review under section 196Y of the VEA. The RMA's declaration of 22 October 2021 was published in the Commonwealth of Australia Gazette on 2 November 2021.
8. On 14 December 2021, the Applicant made a new application to the SMRC seeking a review of the 22 October 2021 RMA declaration. On 10 March 2022, the SMRC published a notification in the Commonwealth of Australia Gazette giving notice under section 196ZB of the VEA that it intended to carry out a review under section 196W of the VEA of all the information available to the RMA when it determined, amended or last amended the Statements of Principles in respect of taking combined hormonal contraceptives as a factor for malignant neoplasm of the breast.

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<sup>1</sup> Section 196Y(2) sets out the required timeframes for a valid request to the SMRC:

(2) The request must be made:

- (a) in the case of a request to review some or all of the contents of a Statement of Principles—within 3 months after the Statement of Principles was made, amended or last amended; or
- (b) if paragraph (a) does not apply—within 3 months after the decision of the Authority.

9. In conducting a review, the Council must review all the information (and only that information) that was available to the RMA when it made the decision under review<sup>2</sup>. This Council received this information from the RMA under section 196K<sup>3</sup> of the VEA. This is information that was used by the RMA as opposed to information that was generally available but not accessed by the RMA. The information that the RMA advised was available to the RMA is listed in **Table 1 of Appendix A (Material before the RMA)**. The information to which the Applicant referred, being information to which the Applicant had provided the RMA, was considered by the Council in reaching its review decision and is noted in **Table 2 of Appendix A (Applicant's Information to the RMA)**.
10. Fundamental to Statements of Principles, and so to a Council review, is the concept of sound medical-scientific evidence<sup>4</sup>. This term is defined in section 5AB(2) of the VEA.

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<sup>2</sup> See *Vietnam Veterans' Association (NSW Branch) v Specialist Medical Review Council and Anor* [2002] 72 ALD 378, per Branson J at [35]:

the SMRC in conducting its review is not only obliged to carry out a review of all of the information that was available to the RMA when it made the decision that gave rise to the request for a review (s196W(2)) but is constrained to conduct its review by reference to that information only.

<sup>3</sup> Section 196K of the VEA requires that the RMA 'send to the Review Council a copy of all the information that was available to it' when it made the decision subject to review.

<sup>4</sup> Sound medical-scientific evidence is defined in section 5AB(2) of the VEA as follows:

Information about a particular kind of injury, disease or death is taken to be sound medical-scientific evidence if:

(a) the information:

- (i) is consistent with material relating to medical science that has been published in a medical or scientific publication and has been, in the opinion of the RMA, subjected to a peer review process; or
- (ii) in accordance with generally accepted medical practice, would serve as the basis for the diagnosis and management of a medical condition; and

(b) in the case of information about how that injury, disease or death may be caused meets the applicable criteria for assessing causation currently applied in the field of epidemiology.

The later requirement is held to mean 'information which epidemiologists would consider appropriate to take into account' see *Repatriation Commission v Vietnam Veterans' Association of Australia NSW Branch Inc.* (2000) 48 NSWLR 548 Spigelman CJ at paragraph 117



11. The Council, when reviewing the information, must determine whether or not there is sound medical-scientific evidence that indicates a reasonable hypothesis<sup>5</sup> connecting the particular injury, disease or death to the relevant service.
12. In a reasonable hypothesis, the evidence 'points to' as opposed to merely 'leaves open' a link between injury, disease or death and the relevant service. In a reasonable hypothesis, the link is not 'obviously fanciful, impossible, incredible or not tenable or too remote or too tenuous.'<sup>6</sup>
13. If Council is of the opinion that a reasonable hypothesis has been raised, the Council proceeds also to determine whether a connection also exists to relevant service on the balance of probabilities<sup>7</sup> (i.e., whether the connection is more probable than not).

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<sup>5</sup> Section 196B(2) of the VEA sets out the 'reasonable hypothesis test':

(2) If the Authority is of the view that there is sound medical-scientific evidence that indicates that a particular kind of injury, disease or death can be related to:

- (a) operational service rendered by veterans; or
- (b) peacekeeping service rendered by members of Peacekeeping Forces; or
- (c) hazardous service rendered by members of the Forces; or
- (ca) warlike or non-warlike service rendered by members;

the Authority must determine a Statement of Principles in respect of that kind of injury, disease or death setting out:

- (d) the factors that must as a minimum exist; and
- (e) which of those factors must be related to service rendered by a person;

before it can be said that a reasonable hypothesis has been raised connecting an injury, disease or death of that kind with the circumstances of that service.

<sup>6</sup> The full Federal Court decision in *Repatriation Commission v Bey* (1997) 79 FCR 364 which cited with approval these comments from the Veterans' Review Board in *Stacey* (unreported 26 June 1985), all of which were in turn cited with approval in the *Moore J* decision at [33].

<sup>7</sup> Section 196B(3) of the VEA sets out the 'balance of probabilities test':

(3) If the Authority is of the view that on the sound medical-scientific evidence available it is more probable than not that a particular kind of injury, disease or death can be related to:

- (a) eligible war service (other than operational service) rendered by veterans; or
- (b) defence service (other than hazardous service) rendered by members of the Forces; or
- (ba) peacetime service rendered by members;

the Authority must determine a Statement of Principles in respect of that kind of injury, disease or death setting out:

- (c) the factors that must exist; and
- (d) which of those factors must be related to service rendered by a person;

before it can be said that, on the balance of probabilities, an injury, disease or death of that kind is connected with the circumstances of that service.

14. In these Reasons, the association for either the reasonable hypothesis test or the balance of probabilities test are referred to as the 'relevant association' as required.
15. The Council exercises its scientific judgement in weighing the evidence about the relevant association.
16. In reaching a decision about the existence or otherwise of a reasonable hypothesis, the Council must consider and evaluate all of the sound medical-scientific evidence. In the situation where there is a single piece of evidence, such as a single study or paper, in support of a reasonable hypothesis, on its own, that may be enough to support the hypothesis. However, this information should be considered with other sound medical-scientific evidence in identifying whether the sound medical-scientific evidence indicates the relation to the medical condition. It is, therefore, important that the Council considers all information in context.
17. From the information that was available to the RMA at the relevant time, the Council considered all information relevant to the scope of this review. In considering the matters within the scope of the review, the Council closely analysed the information, both individually and collectively, taking into consideration both quantitative and qualitative evidence in its evaluations.
18. Information that was not available to the RMA was not considered by the Council in reaching its review decision and is noted in **Table 3 of Appendix A (New Information)**.
19. **Appendix B** sets out further details regarding the composition of the Council for this review and the legislation relating to the making of Statements of Principles.
20. **Appendix C** provides a list of abbreviations used in these reasons.

## WRITTEN AND ORAL SUBMISSIONS

21. This section of the Reasons provides an overview of the written and oral submissions that were invited by the Council to inform their review of Statements of Principles Nos. 96 and 97 concerning malignant neoplasm of the breast.
22. In the notice published in the Commonwealth of Australia Gazette on 10 March 2022, the Council invited the following persons or organisations (persons eligible under section 196Y of the VEA) to make a written submission by 22 April 2022:
  - The Repatriation Commission;
  - The Military Rehabilitation and Compensation Commission;
  - A person eligible to make a claim for a pension under Part II or IV of the VEA;
  - A person eligible to make a claim for compensation under section 319 of the MRCA; and
  - An organisation representing veterans, Australian Mariners, members of the Forces, members of Peacekeeping Forces or their dependants.
23. No submissions were received from the Repatriation Commission, the Military Rehabilitation and Compensation Commission, or other eligible persons or organisations as defined under Section 196Y of the VEA.
24. The Council took into account the written and oral submissions made to it.

### ***Applicant's Submission***

25. The Applicant made an oral submission to the Council on 22 December 2022.
26. The Applicant provided no additional information to that provided in their written submission as listed in **Table 2 of Appendix A (Applicant's Information to the RMA)**.

27. The Applicant contended in the oral submission that combined hormonal contraceptives are considered similar to the combined oral contraceptive pill in medical practice and that the terms are commonly used interchangeably in scientific research. The Applicant referred to the Monographs on the Evaluation of Carcinogenic Risks to Humans by the International Agency on Research on Cancer as an example (IARC 2012) [RMA ID 88981].
28. The Applicant contended that non-oral combined hormonal contraceptives use a more direct route of administration, and therefore, dosages are not comparable to the combined oral contraceptive pill. The Applicant contended that it is the similar mode of action that is related to breast cancer that is important. The Applicant contended that doses had not been considered relevant to the factor regarding combined oral contraceptive pill usage in the Statements of Principles concerning malignant neoplasm of the breast and should not be relevant in relation to non-oral combined hormonal contraceptives.
29. The Applicant contended that the broader term combined hormonal contraceptives is used in Statements of Principles concerning other kinds of injuries, diseases and deaths, but not for the Statement of Principles concerning malignant neoplasm of the breast. The Applicant contended that Statements of Principles should use consistent terms.
30. The Applicant advised that background information had been provided to inform the RMA of how contraceptives are used in practice today. It had been the Applicant's experience that not everyone understood their use in practice. The Applicant stated that they could not find a statement about the information the RMA used to inform their decision in its report.
31. The Council notes selected comments from the Applicant that may be relevant to the functions of the SMRC.
32. The Applicant expressed satisfaction about the opportunity to meet face-to-face with the Council and become familiar with the SMRC decision processes. The Applicant also expressed satisfaction with the composition of the Council.

33. However, the Applicant reported discomfort in responding to medical-scientific questions, feeling unqualified to respond. In future, the SMRC may wish to consider how Applicants should best be engaged in the Council's work and consider the optimal way to engage an Applicant in a discussion of the medical-scientific merit of their submission.
34. The Applicant also suggested the need for improvements in the support and information available in relation to making applications regarding the review of Statements of Principles.
35. Without necessarily endorsing the ideas presented by the Applicant, the Council presents them for consideration by relevant stakeholders.

### **SCOPE OF THIS REVIEW**

36. This section of the Reasons outlines the considerations and decisions made by the Council in defining the scope of their review of Statements of Principles Nos. 96 and 97 concerning malignant neoplasm of the breast.
37. This review considers possible relationships between selected types of contraception and the development of breast cancer (malignant neoplasm of the breast).
38. The Applicant contended that there was sound medical-scientific evidence on which the RMA could have relied to amend Statements of Principles Nos. 96 and 97 concerning malignant neoplasm of the breast, Factor 6(c). The Applicant requested a SMRC review of the decision by the RMA not to replace the term 'combined oral contraceptive pill' with 'combined hormonal contraceptive' in relation to Statements of Principles Nos. 96 and 97, Factor 6(c). During the amendments of 2017 and 2018, no change was made to Factor 6(c). Factor 6(c) includes:

Using a combined oral contraceptive pill for a continuous period of at least three years where:

- (i) use of the combined oral contraceptive pill commenced at least five years before the clinical onset of malignant neoplasm of the breast; and

(ii) where use of the combined oral contraceptive pill has ceased, the clinical onset of malignant neoplasm of the breast has occurred within 15 years of cessation [for Statement of Principles Nos. 96, and occurred within 10 years of cessation for Statement of Principles Nos. 97].

39. The Applicant proposes that Statements of Principles Nos. 96 and 97 concerning malignant neoplasm of the breast should be amended to include non-oral forms of combined hormonal contraceptives, such as the combined vaginal ring, in addition to the combined oral contraceptive pill and that this could be achieved by replacing the term 'combined oral contraceptive pill' with 'combined hormonal contraceptive'. The Applicant reasons that non-oral forms of combined hormonal contraceptives have similar pharmacology, contraindications, complications, side effects and interactions as the combined oral contraceptive pill.
40. On 9 December 2022, the Council wrote to the Applicant advising its preliminary decision on the proposed scope of the review and inviting comment. In developing the scope, and communicating it to various stakeholders, in addition to its soundness as the basis for the present review, the Council was primarily concerned with fairness to the Applicant. No comments were received on the proposed scope of the review.
41. As such, the Council decided that it would have particular regard to whether there was sound medical-scientific evidence on which the RMA could have relied to amend either or both of the Statements of Principles in any or all of the following ways:
- (1) whether there was sufficient sound medical-scientific evidence before the RMA on which to amend the Statements of Principles to include the use of non-oral forms of combined hormonal contraceptives in relation to malignant neoplasm of the breast; and
  - (2) if so, to determine relevant factors for inclusion in those Statements of Principles.

42. The Council acknowledges that a causal relationship between the combined oral contraceptive pill and malignant neoplasm of the breast (including timeframes and dosages) was established under the relevant tests in Statements of Principles Nos. 96 and 97 and was not the subject of contention from the Applicant. In the Council's view, therefore, the relationship between the combined oral contraceptive pill and malignant neoplasm of the breast was not considered a necessary part of the scope of this review.
43. The Council did not consider the relationship between the use of combined hormonal contraceptives and people with a personal history of malignant neoplasm of the breast.

### **COUNCIL'S DECISIONS ON THE RELEVANT SOUND MEDICAL-SCIENTIFIC EVIDENCE**

44. This section of the Reasons outlines the Council's decisions on the sound medical-scientific evidence that were considered to be within the scope of their review of Statements of Principles Nos. 96 and 97 concerning malignant neoplasm of the breast.
45. The Council considered that the sound medical-scientific evidence to be considered in the review should comprise information that:
  - was available to the RMA at the relevant times;
  - was sent by the RMA to the Council under section 196K of the VEA;
  - was considered by the Council to be sound medical-scientific evidence as defined in section 5AB(2) of the VEA; and,
  - in the Council's view, 'touches on' (is relevant to) matters within the scope of review.
46. The Council's final decision on the sound medical-scientific evidence for the review was that it should be comprised of only the information listed in **Table 1 of Appendix A (Material before the RMA)** and **Table 2 of Appendix A (Applicant's information to the RMA)**.

Other information known to the Council from their clinical expertise in this subject matter, as listed in **Table 3 of Appendix A (New information)**, could not be considered but does have the status of the RMA's definition of 'information' and sound medical-scientific evidence in this Review.

## **COUNCIL'S EVALUATION OF THE SOUND MEDICAL-SCIENTIFIC EVIDENCE**

47. This section of the Reasons outlines the Council's evaluation of the relevant sound medical-scientific evidence that it considered to be within the scope of their review of Statements of Principles Nos. 96 and 97 concerning malignant neoplasm of the breast.
48. In forming its decisions on the sound medical-scientific evidence, the Council brings to bear its scientific expertise and judgement.
49. The Bradford Hill criteria (Bradford Hill 1965) and other tools or criteria appropriate to be taken into account by epidemiologists were applied to the information related to causation, as the Council considered appropriate.
50. The Council also considered any methodological limitations or flaws (including such things as statistical power, control of confounders, bias, exposure assessment methods etc.) in the various information.
51. For ease of reference, the Bradford Hill criteria (Bradford Hill 1965) are:
  - strength
  - consistency
  - specificity
  - temporality
  - biological gradient
  - plausibility
  - coherence
  - experiment
  - analogy



52. As described by RMA Researchers Guidelines<sup>8</sup>, additional interpretations of the criteria can sometimes be applied in the study of causation in cases where there is uncertainty about a drug as a possible or probable cause of disease.
53. The Council notes that these criteria are not necessary conditions to establish a causal association. They may provide some evidence of association.

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<sup>8</sup> See Repatriation Medical Authority Guidelines for Researchers. Available from: <http://www.rma.gov.au/assets/What-we-do/87c10e9556/RMA-Researchers-Guidelines-4-February-2022.pdf>

Appendix 3 of the Standard wording for specified factors and definitions guidance on drug factors and lists (page 23) states:

At its April 2018 meeting, the RMA agreed that in situations where there is uncertainty about inclusion of a drug as a possible or probable cause of the disease under investigation, the following criteria will be applied.

Basic criteria (first 3 plus 4 or 5) for limited association (RH)

- (1) Plausible/reasonable temporal association- onset precedes effect within reasonable time frame for that particular drug-disease association; and
- (2) Dechallenge - recovery occurs on drug cessation; and
- (3) At least two independent reports (where no additional criteria are met); and
- (4) Other aetiologies possible but not likely (e.g., other diseases or other drugs); or
- (5) Plausible biological mechanism.

Additional criteria (one or more) for suggestive or convincing association (RH and BOP)

- (6) Rechallenge - response recurs on repeat administration (may be to the same drug or the same class of drug).
- (7) Recovery on administration of an antagonist (e.g., anticholinergics after organophosphate poisoning).
- (8) Proven biological mechanism in that patient (e.g., drug dependent antibodies, positive hypersensitivity testing).
- (9) A significant association is demonstrated in adequately powered epidemiological studies or randomised controlled trials.
- (10) Other aetiologies excluded or highly unlikely.
- (11) Characteristics of the patient are linked to the metabolism of the drug (e.g., presence of a relevant genetic polymorphism, renal or liver impairment).
- (12) Dose-response effect (not always present, there may be a threshold for toxicity or an idiosyncratic reaction).
- (13) Commonality of reports across different reviews (unless there is an indication of perpetuation of single case reports or the reviews are based on loose criteria).
- (14) A large number (usually at least 10) of independent reports.
- (15) The drug is not common and the effect is not common (so that the association is less likely to be coincidental).
- (16) Length of time the drug has been on the market - all but rare adverse effects are likely to be known for older drugs, previously unreported effects may plausibly occur for newer drugs once they are marketed to a wider population.
- (17) The drug is in the same class as a drug which has a probable association.

## **COUNCIL'S CONCLUSIONS ON THE RELEVANT SOUND MEDICAL-SCIENTIFIC EVIDENCE**

54. This section of the Reasons outlines the Council's conclusions on the relevant sound medical-scientific evidence that it considered to be within the scope of their review of the Statements of Principles Nos. 96 and 97 concerning malignant neoplasm of the breast.
55. As established above, the Council accepts that the relationship between the combined oral contraceptive pill and malignant neoplasm of the breast was established under the relevant tests in Statements of Principles Nos. 96 and 97 that Statements of Principles.
56. There is, however, a paucity of evidence relating to the association between drugs in the same class as the combined oral contraceptive pill (i.e. non-oral forms of combined hormonal contraceptives) and malignant neoplasm of the breast.
57. The Council identified one original research paper, considered to be sound medical-scientific evidence, that assessed the association between the use of various hormonal contraception, including non-oral forms of combined hormonal contraceptives, and malignant neoplasm of the breast (Morch et al. 2017) [RMA ID 19959]. Morch et al. (2017) [RMA ID 19959] conducted a national cohort study of women living in Denmark who were aged between 15 and 49 years. National registries provided information on filled prescriptions, breast cancer diagnoses and potential confounders. A total of 1,797,932 women were included in the study population, with a Mean ( $\pm$  standard deviation) follow-up of  $10.9 \pm 5.8$  years. For the main analyses of the study, the relative risk of breast cancer among all current or recent users of any hormonal contraception, compared to never-users, was 1.20 (95% confidence interval, 1.14 to 1.26). Assessment of non-oral combined hormonal contraceptives were sub-analyses of the main study evaluating breast cancer risk and use of any hormonal contraception.

There were few breast cancer events among users of the combined hormonal contraceptive patch (norgestimate) (2 per 10,842 women years for users) and the combined hormonal contraceptive vaginal ring (etonogestrel) (20 per 91,313 women years for users). Compared to never-users, the adjusted relative risks (95% confidence intervals) were 0.85 (0.21 to 3.41) and 0.97 (0.62 to 1.50), respectively. The Council notes the potential for confounding variables not accounted for in the analyses (e.g. screening practices and other associated risk factors for breast cancer) and the limitations in statistical power for the sub-analyses evaluating non-oral combined hormonal contraceptives.

58. The Council concludes that these estimates, which are imprecise (based on the confidence intervals), in relation to the association between non-oral combined hormonal contraceptives and malignant neoplasm of the breast provide insufficient epidemiological evidence to draw conclusions. The Council notes that the absence of sufficient information to establish risk should not lead to a conclusion that there is no risk. Risk remains possible: for example, Morch et al. (2017) [RMA ID 19959] did identify cases of malignant neoplasm of the breast among users of non-oral combined hormonal contraceptives and a small relative risk of malignant neoplasm of the breast among all current or recent users of any hormonal contraception. However, the Council did not consider that these data provide a reasonable hypothesis.
59. The Council identified two letters to the editor about the Morch et al. (2017) [RMA ID 19959] study that suggested potential confounding or interaction effects were unaccounted for in the study (Cramer and Braaten 2018 [RMA ID 10708]; Roberts et al. 2018 [RMA ID 21869]). The Council did not focus its evaluation on these papers, as it considered them to consist of information already considered in evaluating the study by Morch et al. (2017) [RMA ID 19959].

60. The Council noted that non-oral combined hormonal contraceptives (i.e., the combined hormonal contraceptive vaginal ring) are included in the term 'combined hormonal contraceptives' defined by the clinical practice guideline statement from the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG 2019) [RMA ID 25467]. This clinical practice guideline statement included the following definition:

Combined hormonal contraceptives (CHCs), available as combined oral contraceptives (known as 'the pill') and the vaginal ring, are preparations of an oestrogen and a progestagen. CHCs contain ethinyloestradiol (EE), oestradiol valerate, or oestradiol and one of a range of progestogens...The COC [combined oral contraceptive] and vaginal ring work in the same way and are treated similarly in terms of contraindications, complications, side effects and drug interactions. It is assumed that the vaginal ring will offer similar benefits to the COC but because it is relatively new, extensive supporting evidence is lacking. The majority of this statement, unless otherwise stated, refers to both the COC and the vaginal ring.

61. In relation to breast cancer risk, the Council noted that the RANZCOG (2019) [RMA ID 25467] clinical practice guideline statement states:

Evidence is divided on whether use of CHCs [combined hormonal contraceptives] increases the risk of breast cancer. Any increased risk for current users is small and there is no significant difference in risk between ever-users and never-users of CHCs.

62. The Council accepts that the RANZCOG (2019) [RMA ID 25467] clinical guideline statement sets the standard for Australian clinical practice relating to contraceptives, including guidance about its use and statements about its risks. The Council considers this clinical guideline statement to be sound medical-scientific evidence. The Council notes that the Applicant provided this information to the RMA. The Council notes that this information references association studies related to the combined oral contraceptive pill and suggests that the mechanism of action, side effects and risks are similar for oral and non-oral combined hormonal contraceptives (such as the combined vaginal ring). It considers them within a single category of contraceptive, namely combined hormonal contraceptives. However, the Council considered

that while this information supports that non-oral combined contraceptives are of the same drug class as a drug with an established association with malignant neoplasm of the breast (i.e., the combined oral contraceptive pill), they did not consider that these data provide a reasonable hypothesis in the absence of sufficient information to establish an association between non-oral combined hormonal contraceptives and malignant neoplasm of the breast.

63. The Council notes that the term ‘combined hormonal contraceptives’ (including non-oral combined hormonal contraceptives) is used in the information that classifies carcinogens in relation to malignant neoplasm of the breast (IARC 2012 [RMA ID 88981]). The Council considers this information to be sound medical-scientific evidence. The Council notes, as is the case of the RANZCOG (2019) [RMA ID 25467] clinical guideline statement, that this information references association studies related to the combined oral contraceptive pill. The information also references evidence related to the carcinogenic effect of several estrogen-progestogen combinations in different animal models and mammary tumours. The information also proposes that hormone-receptor-mediated responses are probably a necessary mechanism for hormonal carcinogenesis based on experimental studies of combined estrogen-progestogen oral contraceptives and breast cells. However, the Council did not consider that these data provide a reasonable hypothesis in the absence of sufficient information to establish an association between non-oral combined hormonal contraceptives and malignant neoplasm of the breast.

64. Other information that classifies carcinogens in relation to malignant neoplasm of the breast, the US Medical Eligibility Criteria for Contraceptive Use from the Centers for Disease Control, also uses the term 'combined hormonal contraceptives' (CDC 2016). The Council notes that the Applicant provided this information to the RMA. The information states:
- Pending further studies, the evidence available for recommendations about COCs [combined oral contraceptive pills] applies to the recommendations for the combined hormonal patch and vaginal ring.
65. The Council notes the information only makes reference to combined hormonal contraceptives and malignant neoplasm of the breast in reference to people with a personal history of breast cancer, a family history of breast cancer, or an undiagnosed breast mass. The Council notes that the Statements of Principles under consideration (i.e., Statements of Principles Nos. 96 and 97, Factor 6(c)) relate only to clinical onset. The Council, therefore, did not focus its evaluation on this information but notes the use of the term 'combined hormonal contraceptives' is used in this information in the context of informing medical practice.
66. The Council notes that prescribing, product, and consumer information of the non-oral combined hormonal contraceptive NuvaRing®, when establishing precautions and warnings of NuvaRing®, make reference to established malignant neoplasm of the breast risk and use of the combined oral contraceptive pill (MIMS 2020 [RMA ID 19953]; NPS MedicineWise 2021 [RMA ID 19965]; NuvaRing 2020; TGA 2020). The Council notes that medical prescribing information in Australia is subject to peer-reviewed regulatory processes and considers it, generally, to meet the definition of sound medical-scientific evidence. However, the Council considered that while this information supports that non-oral combined contraceptives are of the same drug class as a drug with an established association with malignant neoplasm of the breast (i.e., the combined oral contraceptive pill), they did not consider that these data provide a reasonable hypothesis in the absence of sufficient information to establish an association between non-oral combined hormonal contraceptives and malignant neoplasm of the breast.

67. The Council notes that in relation to the pharmacokinetic properties of the combined hormonal contraceptive vaginal ring, NuvaRing®, prescribing information claims that the NuvaRing® releases relatively lower doses of hormones continuously in comparison to the combined oral contraceptive pill (MIMS 2020) [RMA ID 19953]. The Council acknowledges this data could be interpreted to suggest that lower circulating hormones from non-oral combined hormonal contraceptives, such as the combined hormonal contraceptive vaginal ring, may produce fewer side effects and lower risk of adverse events, such as malignant neoplasm of the breast. However, the Council is of the opinion that this interpretation cannot be drawn from this data alone because greater individual variability in circulating hormones has been reported in users of the combined oral contraceptive pill in comparison to vaginal ring users (van den Heuvel et al. 2005) [RMA ID 28170]. The Council also notes that the basis of the association between the combined oral contraceptive pill and malignant neoplasm of the breast has not been established and could be due to the mechanism of action rather than a dose-response effect. Notably, all combined hormonal contraceptives have the same primary mechanism of action, namely inhibition of ovulation (van den Heuvel et al. 2005) [RMA ID 28170].
68. The Council notes one review paper that advises medical professionals on counselling women about ‘hormonal contraception’ (Marsden 2017) [RMA ID 19939]. The Council did not focus its evaluation on this paper as it considered it to consist of available information it has considered. However, it did note that it used the broader term of ‘hormonal contraception’ in relation to stating: ‘the absolute risk of breast cancer diagnosis associated with exposure to hormonal contraceptives is small.’

69. The Council notes three other papers within the information that was provided to the RMA by the Applicant that are review articles aimed at informing clinical practice on the use of combined hormonal contraceptives and the risk of malignant neoplasm of the breast (Del Pup et al. 2019; McNamee et al. 2013; Zolfarioli et al. 2018). The Council did not focus its evaluation on these papers as it considered them to consist of available information it has considered. However, it did note that two of these reviews consistently use the broader term of ‘combined hormonal contraception’, despite referencing studies of breast cancer risk in relation to the combined oral contraceptive pill (Del Pup et al. 2019; McNamee et al. 2013). In the other review article by Zolfarioli et al. (2018), the Council notes it reinforces the known view that: ‘biological plausibility and clinical data collectively support the conclusion that OC [the combined oral contraceptive pill] slightly increase the risk of breast cancer diagnosis.’
70. The Council notes that the Applicant provided a paper by Westhoff and Pike (2018) that was mentioned in the RMA briefing paper for the RMA meeting in April 2021 and in the RMA decision not to amend the Statements of Principles concerning malignant neoplasm of the breast (RMA (unpublished); RMA 2021). The paper provides commentary following the release of the information by Morch et al. (2017) [RMA ID 19959]. The authors note that the results of the study are largely consistent with previous studies in identifying a small and short-term increase in breast cancer and combined oral contraceptive pill use. The authors also note that it is still unknown whether the effect is biological or diagnostic. The Council did not focus its evaluation on this paper as it considered it to be a review of available information it has considered.
71. The Council acknowledges that the Applicant provided two papers to the RMA (FPV 2020; Kang et al. 2007). These papers were acknowledged in the RMA briefing paper for the RMA meeting in April 2021 and the RMA decision not to amend the Statements of Principles concerning malignant neoplasm of the breast (RMA (unpublished); RMA 2021).



The Council considered these papers were not relevant to the scope of the review because the information did not ‘touch on’ matters related to both combined hormonal contraceptives and malignant neoplasm of the breast. These papers discussed the available types of contraception in Australia, including non-oral combined hormonal contraceptives.

72. The Council acknowledges that the Applicant provided to the RMA two other papers (AIHW 2018; TGA 2015). These papers were not acknowledged in the RMA briefing paper for the RMA meeting in April 2021 or in the RMA decision not to amend the Statements of Principles concerning malignant neoplasm of the breast (RMA (unpublished); RMA 2021). The Council considered these papers were not relevant to the scope of the review because the information did not ‘touch on’ matters related to both combined hormonal contraceptives and malignant neoplasm of the breast. One of these papers, by the Australian Institute of Health and Welfare, describes how breast cancer was the leading cause of death among women across the three Australian Defence Force service status groups combined (AIHW 2018). The other paper, by the Therapeutic Goods Administration, provides an update on the risks of NuvaRing® (a non-oral combined hormonal contraceptive) in relation to arterial and venous thromboembolism (ATE and VTE) (TGA 2015). The information states:

NuvaRing is a contraceptive ring for vaginal use, which releases ethinylestradiol and etonogestrel over a period of three weeks. While NuvaRing is delivered vaginally, the active ingredients are the same as combined hormonal oral contraceptives, and the risks of arterial and venous thromboembolism (ATE and VTE) are similar for all of these products.

73. In summary, due to a lack of evidence, the Council has not identified a causal relationship specifically between non-oral contraceptives and the development of malignant neoplasm of the breast. The only original research study to specifically address the risk of malignant neoplasm of the breast in users of non-oral combined hormonal contraceptives did not identify an increased risk among users or recent users (Morch et al. 2017) [RMA ID 19959].

However, the number of users of non-oral combined hormonal contraceptives in the study was small and likely contributed to the imprecise estimates reported. The RANZCOG (2019) [RMA ID 25467] clinical guideline statement and other prescribing and consumer information (MIMS 2020 [RMA ID 19953]; NPS MedicineWise 2021 [RMA ID 19965]) considers the mechanism of action, side effects and risks similar for oral and non-oral combined hormonal contraceptives (such as the combined hormonal contraceptive vaginal ring). While this information in isolation does not provide a reasonable hypothesis between non-oral combined hormonal contraceptives and malignant neoplasm of the breast, the RANZCOG (2019) [RMA ID 25467] clinical guideline statement is the basis for medical practice across Australia and New Zealand. The clinical guideline statement shows that in generally accepted medical practice, the term 'combined hormonal contraceptives' is used to refer to all combined hormonal contraceptives, not just the combined oral contraceptive pill.

## THE COUNCIL'S CONCLUSIONS ON WHETHER THERE SHOULD BE AN AMENDMENT TO THE STATEMENTS OF PRINCIPLES FOR MALIGNANT NEOPLASM OF THE BREAST

74. Based on the Council's conclusions regarding the relevant sound medical-scientific evidence, this section of the Reasons outlines the Council's conclusions on whether there should be an amendment to the Statements of Principles Nos. 96 and 97 concerning malignant neoplasm of the breast.
75. The Council concluded that there should not be an amendment with respect to non-oral combined hormonal contraceptives in relation to the Statements of Principles Nos. 96 and 97 concerning malignant neoplasm of the breast. This conclusion was based on insufficient evidence available to satisfy the requirements of either or both the reasonable hypothesis test<sup>9</sup> and the balance of probabilities test.<sup>10</sup>
76. Rather, the Council recommends that the RMA undertake a further review of the Statements of Principles having regard to replacing the defined term of 'combined oral contraceptive pill' with the defined term of 'combined hormonal contraceptive'.

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<sup>9</sup> Section 196B(2) of the VEA sets out the 'reasonable hypothesis test':

(2) If the Authority is of the view that there is sound medical-scientific evidence that indicates that a particular kind of injury, disease or death can be related to:

- (a) operational service rendered by veterans; or
- (b) peacekeeping service rendered by members of Peacekeeping Forces; or
- (c) hazardous service rendered by members of the Forces; or
- (ca) warlike or non-warlike service rendered by members;

the Authority must determine a Statement of Principles in respect of that kind of injury, disease or death setting out:

- (d) the factors that must as a minimum exist; and
- (e) which of those factors must be related to service rendered by a person;

before it can be said that a reasonable hypothesis has been raised connecting an injury, disease or death of that kind with the circumstances of that service.

<sup>10</sup> Section 196B(3) of the VEA sets out the 'balance of probabilities test':

(3) If the Authority is of the view that on the sound medical-scientific evidence available it is more probable than not that a particular kind of injury, disease or death can be related to:

- (a) eligible war service (other than operational service) rendered by veterans; or
- (b) defence service (other than hazardous service) rendered by members of the Forces; or
- (ba) peacetime service rendered by members;

the Authority must determine a Statement of Principles in respect of that kind of injury, disease or death setting out:

- (c) the factors that must exist; and
- (d) which of those factors must be related to service rendered by a person;

before it can be said that, on the balance of probabilities, an injury, disease or death of that kind is connected with the circumstances of that service.

77. The Council formed a view that the classification of contraceptives as relevant to the possible causation of malignant neoplasm of the breast that appears in the Statements of Principles Nos. 96 and 97 as 'combined oral contraceptive pill' does not reflect the current use of the term in medical practice. The Council, with its relevant clinical expertise, believes that the RANZCOG (2019) [RMA ID 25467] clinical guideline statement best reflects generally accepted medical practice in Australia on this topic. The term used in this clinical guideline statement is 'combined hormonal contraceptives'.
78. The Council formed a view that while it is not currently possible to determine a relevant association for non-oral combined hormonal contraceptives and malignant neoplasm of the breast, a further review of the epidemiological study of relationships between contraceptives and a variety of health outcomes may produce different results if the classification of contraceptives were to reflect current medical practice. In forming this view, the Council started from the position that there is already an established causal relationship between the combined oral contraceptive pill and malignant neoplasm of the breast, as established by the Statements of Principles Nos. 96 and 97. It also took into account sound medical-scientific evidence<sup>11</sup> that considers non-oral combined hormonal contraceptives to be of the same class as the combined oral contraceptive pill (IARC 2012 [RMA ID 88981]; MIMS 2020 [RMA ID 19953]; NPS MedicineWise 2021 [RMA ID 19965]; RANZCOG 2019 [RMA ID 25467]), and that cases of malignant neoplasm of the breast were reported by the only study that has investigated non-oral combined hormonal contraceptives and malignant neoplasm of the breast (Morch et al. 2017) [RMA ID 19959].

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<sup>11</sup> Sound medical-scientific evidence is defined in section 5AB(2) of the VEA as follows:

Information about a particular kind of injury, disease or death is taken to be sound medical-scientific evidence if:

(a) the information:

- (i) is consistent with material relating to medical science that has been published in a medical or scientific publication and has been, in the opinion of the RMA, subjected to a peer review process; or
- (ii) in accordance with generally accepted medical practice, would serve as the basis for the diagnosis and management of a medical condition; and

(b) in the case of information about how that injury, disease or death may be caused meets the applicable criteria for assessing causation currently applied in the field of epidemiology.

The later requirement is held to mean 'information which epidemiologists would consider appropriate to take into account' see *Repatriation Commission v Vietnam Veterans' Association of Australia NSW Branch Inc.* (2000) 48 NSWLR 548 Spigelman CJ at paragraph 117

## COUNCIL'S ANALYSIS OF NEW INFORMATION

79. This section of the Reasons outlines the Council's analysis of evidence that it considered to be related to the use of non-oral forms of combined hormonal contraceptives and malignant neoplasm of the breast but was not available to (not before) the RMA at the relevant times.
80. In conducting a review, the Council should not consider information that was not available to (not before) the RMA at the relevant times.
81. The Council has neither the capacity nor the jurisdiction to perform an investigative function, including undertaking a comprehensive literature search. However, because of the Councillors' specialist expertise in this kind of injury, disease or death, the Council was aware of some new information (listed in **Table 3 of Appendix A (New Information)**) which it considered on a preliminary basis.
82. The Council considered the new information to determine whether, in the Council's view, it warranted the Council making any recommendations to the RMA under section 196W(5) of the VEA.
83. In the Council's view, any such recommendation should only be made by the Council if it formed the view that the new information comprised sound medical-scientific evidence as defined in section 5AB(2) of the VEA and:
  - in the Council's view, 'touched on' (was relevant to) the contended factor; and
  - could potentially satisfy the reasonable hypothesis and/or balance of probabilities tests.
84. The Council is aware of information from other authorities around the world, but these were not available to the RMA at the relevant time. These other pieces of information would have been directly relevant to the current review.

85. In particular, the Council notes the availability of other international guidelines that are consistent with the RANZCOG (2019) [RMA ID 25467] clinical guideline statement (FSRH 2019). The FSRH (2019) guidelines state:

Women should be advised that current use of CHC [combined hormonal contraceptives] is associated with a small increased risk of breast cancer which reduces with time after stopping CHC.

86. The Council also notes that the term 'combined hormonal contraceptives' is the currently preferred term used in documents that serve as the basis for contraceptive guidance internationally (Black et al. 2017; FSRH 2016; FSRH 2019; WHO 2015). These documents advise that combined hormonal contraceptives, including non-oral forms of combined hormonal contraceptives, should be considered to have the same risks as the combined oral contraceptive pill until new data become available. While these documents were only considered on a preliminary basis, the Council considered that it did serve to support and not contradict its recommendation to the RMA to undertake a further review of the Statements of Principles having regard to replacing the defined term of 'combined oral contraceptive pill' with the defined term of 'combined hormonal contraceptive', as the isolated term 'combined oral contraceptive pill' does not reflect the current classification of contraceptives in medical practice

## **DECISION**

87. The Council made the declarations and recommendations summarised in Declaration and Reasons for Decisions.

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