

5.27 WARFARIN

Tablet containing warfarin sodium, 1mg, 2mg, 5mg

Warfarin APOTEX[®],

Apotex Pty Ltd.

1 Purpose of Application

- 1.1 The minor submission requested a General Schedule unrestricted benefit listing for Warfarin APOTEX[®] 1mg, 2mg and 5mg tablets.
- 1.2 The minor submission also requested that Warfarin APOTEX[®] 1mg, 2mg and 5mg tablets be marked as equivalent (i.e. 'a' flagged) to warfarin Coumadin[®] brand of tablets.

2 Requested listing

- 2.1 The minor submission requested a General Schedule unrestricted benefit listing for Warfarin APOTEX[®] 1mg, 2mg and 5mg tablets, consistent with the listing of the same strengths of Coumadin[®] and Marevan[®] brands of warfarin.
- 2.2 The minor submission indicated that Warfarin APOTEX[®] is bioequivalent to the current PBS listed brand Coumadin[®], and therefore sought for these brands to be 'a' flagged. The minor submission did not demonstrate bioequivalence with the Marevan[®] brand of warfarin. Coumadin[®] and Marevan[®] are the two brands of warfarin currently listed on the General Schedule with an Unrestricted benefit; Coumadin[®] and Marevan[®] are not 'a' flagged.
- 2.3 As such, the minor submission requested that the current 'Caution' note in the warfarin listing be changed from "The listed brands have NOT been shown to be bioequivalent and should not be interchanged" to "The Marevan[®] brand has NOT been shown to be bioequivalent and should not be interchanged".
- 2.4 The pack size, maximum quantity and number of repeats requested in the minor submission are consistent with the current listing of warfarin Coumadin[®]. The Active Pharmaceutical Ingredient (API) used in Coumadin[®] is 'warfarin sodium amorphous', whereas the API for Warfarin APOTEX[®] is 'warfarin sodium clathrate'. However, the TGA has assessed these to be bioequivalent.

For more detail on PBAC's view, see section 7 "PBAC outcome"

3 Background

- 3.1 Warfarin APOTEX[®] was ARTG registered on 27 April 2016 for the following indications:
 - prophylaxis and/or treatment of venous thrombosis and its extension and pulmonary embolism;

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- prophylaxis and/or treatment of the thromboembolic complications associated with atrial fibrillation; and
- for use as an adjunct in the treatment of coronary occlusion.

The registered indications for Warfarin APOTEX[®] are identical to those of the currently PBS listed Coumadin[®] and Marevan[®] brands of warfarin tablets.

- 3.2 The TGA accepted that Warfarin APOTEX[®] and Coumadin[®] are bioequivalent, but recommended that the sponsor for Warfarin APOTEX[®] address the risk of potential medication error via a risk management plan. For further details on the risk management plan presented in the minor submission, see “Quality use of medicines” section below.
- 3.3 A submission seeking PBS listing for Warfarin APOTEX[®] has not been considered by the PBAC previously.
- 3.4 Warfarin is a drug with narrow therapeutic index, i.e. a small change in dose can have a significant impact on pharmacodynamic response. Specifically for warfarin, the effectiveness and safety profile of the drug is dependent on careful dose titration balancing between the risk of stroke and the risk of bleeding. As such, brand substitution of drugs with narrow therapeutic index raises potential quality use of medicines (QUM) issues. (See “Quality use of medicines” section below).
- 3.5 Narrow therapeutic index drugs have been previously listed on the PBS with bioequivalent brands ‘a’ flagged to each other (e.g. digoxin).
- 3.6 At present, listing of a new generic brand would trigger a 16% price reduction across all PBS-listed brands of the drug.
- 3.7 Further background on warfarin is provided in the “Committee-in-confidence” section.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

4 Clinical place for the proposed therapy

- 4.1 Warfarin APOTEX[®] is proposed to directly substitute for Coumadin[®], as these brands have the same TGA approved indications.

5 Comparator

- 5.1 The minor submission nominated Warfarin Coumadin[®] as the main comparator. The PBAC considered that the proposed comparator was appropriate, since the submission sought ‘a’ flagging of Warfarin APOTEX[®] and Coumadin[®].

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item as it was a minor submission.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The minor submission presented the following clinical trials as pivotal and supportive evidence of bioequivalence of Warfarin APOTEX[®] and Coumadin[®] (Table 1).

Table 1: Trials presented in the submission

Study ID	Description	Publication citation
WA8300	Bioequivalence study, conducted with Australian-branded Warfarin APOTEX [®] and Coumadin [®] tablets. This study was a single dose, 2-way cross over study conducted in healthy volunteers in the fasted state.	Unpublished data
WATB02	To determine the relative bioavailability of warfarin from two drug products in a 2-way cross-over comparative bioavailability study under fasting conditions; 10 mg tablets.	Unpublished data
WATB03	To determine the relative bioavailability of warfarin from two drug products in a 2-way cross-over study under fed conditions; 10mg tablets.	Unpublished data
WATB04	Bioavailability study to compare warfarin 1mg tablets (APOTEX, Inc.) with that of Coumadin [®] tablets (DuPont Pharma) in the fasted state. A single-dose, 2-way, randomised cross over study when dosed (2x1mg) after an overnight fast.	Unpublished data
WATB05	Bioavailability study to compare warfarin 1mg tablets (APOTEX, Inc.) with that of Coumadin [®] tablets (DuPont Pharma) in the fed state. A single-dose, 2-way, randomised cross over study when dosed (2x1mg) after a high fat meal preceded by an overnight fast.	Unpublished data
WA6231	Double-blind, single dose, standard randomised 2-way cross over relative bioavailability study performed on healthy adult males under fasting conditions. Test formulation: warfarin sodium tablets 10mg (APOTEX Inc.). Reference formulation: Coumadin [®] Tablets 10mg (Bristol-Myers Squibb, Canada)	Unpublished data
WA6232	Double-blind, single dose, standard randomised 2-way cross over relative bioavailability study performed on healthy adult males under fed conditions. Test formulation: warfarin sodium tablets 10mg (APOTEX Inc.). Reference formulation: Coumadin [®] Tablets 10mg (Bristol-Myers Squibb, Canada)	Unpublished data
Pereira et al 2005	“Are brand-name and generic warfarin interchangeable? Multiple N-of-1 randomized, crossover trials.” Multiple n-of-1 randomised, double-blind, crossover trials switched outpatients (N = 7) between a generic warfarin formulation (Apo-warfarin) and Coumadin [®] over 30 weeks. Study patients took each drug for five 3-week periods, with international normalized ratio (INR) measurements taken twice per period. Inter- and intra-patient differences between generic warfarin and Coumadin [®] were compared, and overall study patient results were compared with those of a Coumadin [®] control group.	Annals of Pharmacotherapy 39: 1188-93.

Source: Table 6 of the submission.

6.4 The basis of the minor submission’s request was evidence of bioequivalence from the pivotal study WA8300.

- 6.5 The minor submission indicated that the study design to assess bioequivalence was developed in accordance with the European Medical Agency (EMA) guideline on investigation of bioavailability and bioequivalence. In addition, since warfarin is a drug with narrow therapeutic index, the accepted range of confidence interval (CI) was tightened, such that the formulations were considered bioequivalent when the 90% CI of the test was within 90% to 111.11% of the reference formulation. The submission stated that this was accepted by the TGA.
- 6.6 The minor submission also presented supportive evidence from six bioequivalence studies conducted in Canada (Table 1). All six studies met the predefined criteria for bioequivalence. The bioequivalence criteria for area under the curve (AUC) was 80-125% in four of the six Canadian studies, however the minor submission claimed that the results could have also achieved the tighter criteria of 90-111.11%.
- 6.7 The minor submission also presented evidence from a repeat randomisation (switching study) conducted in Canada. No statistically significant differences were observed in INR levels on switching patients from Coumadin[®] to Warfarin APOTEX[®] (Pereira *et al.* 2005, Table 1).

Clinical claim

- 6.8 The submission claimed that based on the evidence provided, Warfarin APOTEX[®] and Coumadin[®] were bioequivalent.
- 6.9 The PBAC noted that this claim was supported by the TGA assessment, which considered Warfarin APOTEX[®] and Coumadin[®] to be bioequivalent.

Economic analysis

- 6.10 The minor submission did not present a formal economic analysis. However, a cost-minimisation approach was implied as Warfarin APOTEX[®] was priced on an interchangeable basis with Coumadin[®]. The statutory 16% price reduction for Coumadin[®] was taken into account in calculating the ex-manufacturer price for Warfarin APOTEX[®], with the assumption that Warfarin APOTEX[®] will be the first generic brand of warfarin to be listed on the PBS.

Estimated PBS usage & financial implications

- 6.11 The submission presented an estimated net cost to the Government health budgets based on the following assumptions:
- 5 additional INR tests per patient per brand switch;
 - 50% INR testing conducted would be MBS funded; and
 - an average treatment duration of 6 months.
- 6.12 Based on the first two assumptions, an estimated MBS cost of additional INR testing was factored into the calculation for net cost to government health budgets. These assumptions were based on brand switching, rather than random brand substitution at the pharmacy level.
- 6.13 The minor submission assumed a market share model, with Warfarin APOTEX[®]

being substituted one-for-one with Coumadin[®]. Therefore, although no difference in usage were presented, the submission claimed a cost saving to the government health budget in the five-year forward estimates via the statutory price reduction by listing a generic brand, despite the additional cost of MBS-funded INR testing (Table 3).

Table3: Summary of net cost to government health budgets

	Year 1	Year 2	Year 3	Year 4	Year 5
Net cost to PBS/RPBS	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
PBS	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
RPBS	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Net cost to MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to government health budgets	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]

6.14 At year 5, the estimated net save to the PBS would be less than \$10 million per year.

6.15 The PBAC considered that the financial estimates did not reflect what would occur in practice if Warfarin APOTEX was 'a' flagged, and noted that the difference in the rate and cost of additional INR testing was uncertain, as it relied on patients being informed that they should get additional INR testing, and was dependent on whether the testing occurred in a setting eligible for MBS rebate.

Quality use of medicines

6.16 The PBAC noted that the TGA recommended that the sponsor of Warfarin APOTEX[®] address potential QUM issues through a risk management plan.

6.17 The potential QUM issues identified were:

- Since bioequivalence of Warfarin APOTEX[®] and Warfarin Marevan[®] has not been demonstrated, these products should not be substituted.
- Increased monitoring may be required to minimise the potential risk to the patient.
- Episodes of switching may need to be kept to a minimum.

The PBAC considered that 'a' flagging warfarin APOTEX[®] would exacerbate some of these QUM issues as it would enable switching between brands to occur without any limitation on the number of times, and potentially without the need for additional testing being identified.

6.18 The minor submission indicated that support material for patients encourages patients to note the colour and strength of their regular tablets, and to continue to take the tablets they were first prescribed. The submission claimed that this is important, as it assists patients to differentiate between Warfarin Coumadin[®] or Warfarin Marevan[®], since these are *not* bioequivalent, and are available in a different range of tablet strengths (2mg tablet is unique to Coumadin[®]; 3mg is unique to Marevan[®]). The minor submission claimed that Warfarin APOTEX[®] has been developed to resemble Coumadin[®] tablets in shape, colour and range of strengths, to prevent confusion at the patient level.

- 6.19 The minor submission claimed that the responsibility of ensuring safe brand substitution rests with pharmacists, who are provided certain guidelines from The Pharmacy Board of Australia on QUM practices¹ relating to:
- the supply of medicines that have a narrow therapeutic index (e.g. cytotoxics and other immunosuppressants, warfarin, digoxin, insulins);
 - the taking of medicines that require therapeutic monitoring or specific biochemistry or haematology monitoring (e.g. warfarin and other anticoagulants, antithrombotics, digoxin, clozapine); and
 - when the brand of medicine has changed.
- The PBAC noted that, although pharmacists have an important role in providing support to patients, they are not required to contact the prescriber to notify them of a brand substitution for 'a' flagged items on the PBS, but that the risk management plan relies on this contact occurring.
- 6.20 The PBAC noted that the Precautions section of the Warfarin APOTEX[®] Product Information (PI) states that "To minimise the possibility of adverse effects, substitution between Coumadin and Warfarin APOTEX[®] should only occur if the prescriber and patient are aware of the change and a plan for INR monitoring is in place. It is recommended that vigilant INR testing should be conducted during the cross-over period." The PBAC noted that the risk management plan around Warfarin APOTEX[®] was extensive and considered that 'a' flagging Warfarin APOTEX[®] would contradict the intention of both the risk management plan and the Precautions outlined in the PI, by making it possible for substitution to occur regularly and without the knowledge of the prescriber.
- 6.21 The National Prescribing Service lists warfarin among a range of drugs that should not be substituted at the pharmacy level without permission from the doctor².
- 6.22 The PBAC noted that in the case of warfarin there were already two brands listed on the PBS, and Warfarin APOTEX would only be 'a' flagged to one of these. The PBAC considered that this additional complexity would introduce an even greater risk of confusion for patients, and therefore a high risk of adverse outcomes. Furthermore, the PBAC considered that there was no clinical need for a third brand of warfarin to be available on the PBS, particularly given the risks associated with confusion.
- 6.23 The PBAC noted that utilisation of warfarin was decreasing over time and considered that it was possible the patients currently taking warfarin represented a more vulnerable population, where the impacts of confusion would be even greater.

COMMITTEE-IN-CONFIDENCE

[REDACTED]

¹ Pharmacy Board of Australia, 2015. *Guidelines for Dispensing of Medicines*.

² NPS MedicineWise. <http://www.nps.org.au/media-centre/media-releases/repository/consumer-should-be-centre-of-care-when-offering-alternative-medicine-brands>

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

END COMMITTEE-IN-CONFIDENCE

For more detail on PBAC's view, see section 7 "PBAC outcome"

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of Warfarin APOTEX[®] in the context of potential safety and QUM issues identified.
- 7.2 The PBAC considered that, due to the narrow therapeutic index of warfarin, the listing of additional brands for warfarin would significantly increase the potential risk of adverse outcomes, and that it would likely cause confusion and distress to patients, particularly because it is important that substitution does not occur between the two currently listed brands of warfarin, Coumadin[®] and Marevan[®].
- 7.3 The PBAC noted the sponsor's extensive risk management plan, and considered that 'a' flagging would contradict some of the risk mitigation measures outlined in the plan. The PBAC considered that in practice, there was a strong likelihood that prescribers would not be informed each time a change of brand occurs at the pharmacy level since 'a' flagging would enable 'brand substitution', instead of 'brand switching', without any obligation on the pharmacist to notify the prescriber.
- 7.4 The PBAC noted that there was considerable uncertainty surrounding the number of additional INR tests that would occur in practice, as it was dependent on patients being advised of the recommendation for additional testing following substitution, and

the prescriber being notified. The PBAC also considered that even in the instances where this occurred, it may be that a patient's regular testing schedule would be moved forward, rather than *additional* INR tests being conducted.

- 7.5 The PBAC noted that since the introduction of novel oral anticoagulants, fewer patients were being prescribed warfarin, and it is possible that the patients now taking warfarin are a more vulnerable patient population, in which the impact of confusion, or substitution occurring without additional INR testing, could have a more serious effect. The PBAC also noted that the trend in reducing rates of warfarin prescribing is likely to continue.
- 7.6 The PBAC considered that the current availability of two brands of warfarin which are not substitutable poses an additional risk of confusion, and allowing 'a' flagging between Warfarin APOTEX[®] and one of the available brands and not the other increased the risk of inappropriate substitution between the brands that are not bioequivalent. The PBAC further considered that there was no clinical need for a third brand of warfarin on the PBS, and that the risk of confusion outweighed any potential gain.
- 7.7 The PBAC considered that, although 'a' flagging has been approved for other drugs with a narrow therapeutic range, the potential impact of inadequate control of warfarin dose was much higher, and more likely to be fatal than for other drugs.
- 7.8 The PBAC noted that this submission is not eligible for an Independent Review, as the submission requested for PBS listing for a brand of an already listed drug.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

The sponsor had no comment.