

Formulary Considerations Related to Warfarin Interchangeability

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INTRODUCTION

For years, Coumadin (DuPont Pharma Inc., Mississauga, Ontario) was the only warfarin product marketed in Canada. Recently, 2 additional warfarin products have received approval for sale in Canada: Taro-Warfarin (Taro Pharmaceuticals Inc., Bramalea, Ontario) and Apo-Warfarin (Apotex Inc., Weston, Ontario).

Warfarin is a drug with a narrow therapeutic range, as defined by Health Canada¹: its ratio of minimum toxic concentration to median effective concentration is less than or equal to 2. In addition, warfarin has an unpredictable dose response; therefore, close therapeutic monitoring is required for optimal antithrombotic effect with minimal bleeding complications. Because minor dose changes can result in clinically significant changes in the international normalized ratio (INR), the issue of equivalence between brand name and generic warfarin products requires careful evaluation.² Table 1 presents several characteristics used in assessing the degree of equivalence between the various warfarin formulations now available in Canada. These variables were used in deciding on the warfarin product to be included on the formulary at the authors' hospital.

THERAPEUTIC CONSIDERATIONS

Content Uniformity

To determine content uniformity, single tablets are assayed for the amount of active ingredient, which is compared with the labelled strength. Content uniformity requirements assure the clinician of consistency of tablet strength within and among batches of a drug.

The United States Pharmacopoeia (USP) specifies that 10 tablets from any batch must contain 85% to 115% of the labelled strength, with a standard deviation of less than 6%. If one tablet falls outside this range, then 20 more tablets must be tested.³ For these 30 tablets, the standard deviation must be less than 7.8%, and all tablets must be within 75% to 125% of the labelled strength, with only one tablet less than 85% or greater than 115% of the labelled strength.

All 3 manufacturers of warfarin use more stringent specifications for tablet uniformity than those designated by the USP.^{4,†} For all 3 manufacturers, the initial 10 tablets tested must contain 92.5% to 107.5% of labelled strength, and the standard deviation must be less than 3%. If one tablet falls outside this range, then 20 more tablets must be tested. For these 30 tablets, the standard deviation must be less than 3.9%, and all tablets must be within 87.5% to 112.5% of labelled strength; only one tablet with a value less than 92.5% or greater than 107.5% is allowed.⁵

It is noteworthy that Apotex originally followed USP specifications for warfarin tablet uniformity. However, after the company's court case with the Ministry of Health for Alberta and the Expert Committee on Drug Evaluation and Therapeutics in late 2001, it agreed to follow the same stringent content uniformity specifications used by DuPont Pharma and Taro Pharmaceuticals.^{6,7}

*Peter Gingras, Director of Scientific Administration, Apotex Inc. Personal communication, April 2002.

†Basim Zeineldin, Product Manager, Taro Pharmaceuticals Inc. Personal communication, March 2001.



Table 1. Comparison of Warfarin Formulations Available in Canada

Characteristic	Coumadin	Taro-Warfarin	Apo-Warfarin
Manufacturer	DuPont Pharma	Taro Pharmaceuticals Inc.	Apotex
Content uniformity	92.5% to 107.5% of labelled strength	Follows DuPont specifications	Follows Dupont specifications
Meets Health Canada mean bioequivalence standards	Reference drug	Yes	Yes
Individual bioequivalence	Reference drug	Yes	No data
Therapeutic equivalence	Reference drug	No data	No data
Unit-dose packaging	Yes	No	No
Cost per tablet* (and VGH cost per tablet), \$			
1 mg	0.32 (0.10)	0.20	0.20
5 mg	0.36 (0.08)	0.17	0.17

VGH = Vancouver General Hospital.

*Manufacturer's book price.

Mean Bioequivalence

To establish bioequivalence for a drug with a narrow therapeutic range, the test drug must meet certain bioequivalence standards relative to the reference drug. Health Canada has developed a set of standards that are used to determine bioequivalence in Canada: the 95% confidence interval of the pharmacokinetic parameters of area under the curve and maximum concentration of the test drug must be within 80% to 125% of the value of the reference drug in healthy subjects, in both fed and fasting states.⁸ These standards are more stringent than for uncomplicated drugs, for which the confidence interval is 90%.¹ Both Taro-Warfarin and Apo-Warfarin meet the Health Canada standards for drugs with narrow therapeutic range.*†

Individual Bioequivalence

Because drug pharmacokinetics differ among individual patients, individual bioequivalence studies are sometimes used to provide more assurance that reference and test products are interchangeable. By measuring individual pharmacokinetic parameters, the possibility of subject-by-formulation interactions during the absorption processes can be determined. No individual bioequivalence data exist for the Apotex brand of warfarin. One crossover study has been

published for a comparison of Taro-Warfarin with Coumadin in 23 patients.⁹ This study confirmed the findings of previous mean bioequivalence studies and indicated that Taro-Warfarin and Coumadin are equivalent in terms of their pharmacokinetic parameters.

Therapeutic Equivalence

The therapeutic equivalence of warfarin products is assessed by comparing INR values in crossover studies involving patients receiving long-term warfarin therapy. These studies test the therapeutic outcomes when warfarin products are switched, whereas the other parameters mentioned thus far measure pharmacokinetic or surrogate markers of product equivalence.

Therapeutic equivalence studies have not been performed for the Taro or Apotex products. However, 3 studies involving a total of approximately 400 patients have been conducted with a generic formulation available in the United States, Barr generic warfarin sodium (Barr Laboratories, Pomona, New York).¹⁰⁻¹² Two studies^{10,11} had observer-blinded, randomized, crossover designs, and the third study¹² had an open-label, nonrandomized design. All 3 studies demonstrated comparable efficacy and safety for Barr generic warfarin sodium and Coumadin. Bleeding complications were not statistically different between the 2 products. As well, dosage adjustments were required no more frequently with the Barr product than with Coumadin. A randomized crossover comparison of Coumadin with a different generic warfarin product available in the United States (Apothecon Inc., Princeton, New Jersey) also found equivalent anticoagulation with respect to changes in dosage and INR in patients with atrial fibrillation.¹³

*Peter Gingras, Director of Scientific Administration, Apotex Inc. Personal communication, April 2002.

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These results suggest that extra INR monitoring is unnecessary when patients are switched from Coumadin to generic formulations. However, some case reports have documented subtherapeutic INRs associated with switching from Coumadin to Barr generic warfarin sodium.⁴ Therapeutic equivalence studies and case reports involving small numbers of patients and short duration of therapy are difficult to interpret, as many factors affect a patient's response to warfarin, and these may not be adequately controlled in such limited studies.

Cost and Unit-Dose Packaging

The price of Coumadin at the authors' institution is about half that of the generic formulations (Table 1). DuPont Pharma offers unit-dose packaging for their product, but neither Taro Pharmaceuticals nor Apotex offers this packaging option yet.

INTERCHANGEABILITY OF WARFARIN IN CANADA

In Quebec, Newfoundland, and Nova Scotia, oral anticoagulants are considered non-interchangeable, whereas in British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, and New Brunswick, the 3 brands of warfarin are considered interchangeable.

CONCLUSIONS

The warfarin products of both Taro Pharmaceuticals and Apotex meet Health Canada requirements for bioequivalence with Coumadin, and both companies follow more stringent content uniformity specifications than outlined by USP (similar to those used by DuPont Pharma for Coumadin). Published studies of therapeutic equivalence with adequate patient numbers and duration of therapy are lacking for both generic products. Such studies could clarify the need for supplementary INR monitoring when patients are switched from one brand to another. However, where close monitoring of INR and clinical status is to be expected, as in a hospital setting, switches between brands should not pose any therapeutic problems. Accordingly, the Drugs and Therapeutics Committee at the authors' institution has deemed that all warfarin brands should be considered interchangeable. Coumadin has been retained on the formulary for several reasons: most patients were receiving this preparation in the community before entering hospital, it has unit-dose

packaging, and there is no cost advantage to changing to another brand.

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Disclaimer

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