

the  **DBL** report
UPDATE

Update, December 2000

An Official Accompaniment to
the Alberta Health Drug Benefit List (AHDBL)

The Expert Committee on Drug Evaluation and
Therapeutics (ECDET)

produced by Alberta Blue Cross

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Interchangeability of Warfarin Sodium Preparations

On December 1, 2000, the warfarin sodium preparations, COUMADIN and TARO-WARFARIN will be designated as interchangeable drug products on the Alberta Health and Wellness Drug Benefit List (AHWDBL).

The designation of interchangeability of these warfarin sodium preparations follows a long and comprehensive review by the Expert Committee on Drug Evaluation and Therapeutics. In their review, the Expert Committee considered comparative bioavailability data provided by rigorous bioequivalence studies, manufacturing and quality control specifications, and prior decisions by federal regulatory bodies such as the Canadian Therapeutic Products Programme (TPP) and the US Food and Drug Administration (FDA). They also reviewed information from Dupont Pharma Inc. and Taro Pharmaceuticals Inc. provided as a result of a challenge by Dupont Pharma Inc. to the potential interchangeability of these products.

The products TARO-WARFARIN and COUMADIN are bioequivalent. Bioequivalence study design requirements and standards for narrow therapeutic range drugs, in accordance with the TPP Directive 'Standards for Comparative Bioavailability Studies Involving Drugs with a Narrow Therapeutic Range - Oral Dosage Forms', were met in all instances. TARO-WARFARIN and COUMADIN are manufactured according to the same stringent manufacturing specifications that exceed USP requirements. It should be noted that both the TPP and FDA have declared equivalence between TARO-WARFARIN and COUMADIN.

In the determination of bioequivalence and interchangeability of drug products, consideration is given to differences in formulations and how such differences may affect the absorption of a drug. Care must be taken not to inappropriately transfer therapeutic concerns about the characteristics of a drug to the determination of bioequivalence if there are no significant absorption or formulation differences detected. Warfarin sodium is a highly permeable, soluble drug which has idiosyncratic elimination profiles, but does not have any documented absorption problems. Furthermore, it is available in the simple formulation of an uncomplicated, regular release tablet.

Statements in the COUMADIN product monograph and labeling that recommend additional INR testing or monitoring should occur if generic warfarin is substituted for COUMADIN were made at a time when there were warfarin

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products in the marketplace that were not bioequivalent or therapeutically equivalent to COUMADIN (e.g. warfarin potassium).

At the conclusion of their review, the Expert Committee expressed confidence that TARO-WARFARIN can be substituted for COUMADIN with the full expectation that it will produce the same clinical effect and safety profile. The Expert Committee felt that additional INR testing over and above that normally required for routine patient monitoring is not warranted when TARO-WARFARIN is substituted for COUMADIN.

In the future, additional generic warfarin products may become available in the marketplace. Each of these products will be reviewed as stringently as TARO-WARFARIN has been. Theoretic concerns about the therapeutic risks of new generic products being compared to the innovator, and not to other generics, will be dealt with as each new product is reviewed.