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All formulary changes and policy/procedure updates have been approved by the Drugs and Therapeutics (D&T) Committee and Medical Advisory Council (MAC).

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## *Changes to Formulary*

### **Additions**

- 1. Daclizumab injection (Zenapax®)**
  - Monoclonal antibody
  - Management of acute graft vs host disease
- 2. Dipyridamole 200mg extended release + ASA 25mg capsules (Aggrenox®)**
  - Antiplatelet drugs indicated for prevention of stroke in patients who have had a previous stroke or transient ischemic attack (TIA)
  - See page 4 for review

### **3. Iron Polysaccharide Complex 150mg capsules (Niferex®)**

- Once daily oral iron preparation

**Table 1. Comparison of Formulary Oral Iron Products**

Iron Salt	Strength	Elemental Iron	Cost/~180mg Elemental Iron*
Ferrous Sulphate	300mg	60mg	\$0.03 (3 tablets)
Ferrous Gluconate	300mg	36mg	\$0.05 (5 tablets)
Iron Poly-saccharide (Niferex®)	150mg	150mg	\$0.19 (1 tablet)

\*recommended dose to treat iron deficiency

### **4. Olanzapine dissolvable tablets 5mg, 10mg (Zyprexa® Zydys)**

- Oral disintegrating tablet that dissolves on contact with saliva
- Used to facilitate compliance in patients who “cheek” their medication or those who have difficulty swallowing oral tablets
- May be placed in mouth or dispersed in water or other beverage for administration
- Bioequivalent to olanzapine coated tablets with similar rate and extent of absorption

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Find us on the Web at [www.vhpharmsci.com](http://www.vhpharmsci.com)

### 5. Replavite®

- Oral multivitamin preparation containing Vitamins B & C
- Replaces Diavite®; only difference is that Replavite® contains vitamin C 100mg compared to 60mg for Diavite®

## Deletions

The following drugs have been deleted by the manufacturer:

### 1. Diavite®

- Alternative: Replavite®

### 2. Mumps Skin Test Antigen

- Alternatives: Trichophyton, Candida

### 3. Ethanolamine injection

- Alternatives: Ethyl Alcohol 100%, Sodium tetradecyl (Thromboject®)

### 4. Echothiophate Iodide eye drops (Phospholine Iodide®)

## Updated Policies/Procedures

### 1. Removal of Concentrated Potassium Chloride (KCl) Intravenous Vials

It is recognized that the availability of concentrated KCl vials (i.e. 2mEq/mL—10mL) as wardstock on nursing units may lead to avoidable medication errors. Errors have occurred as a result of incorrect preparation and inadequate mixing of KCl solutions. Several patient deaths have occurred in Canada due to the accidental administration of concentrated KCl in intravenous (IV) solutions. As a result, removal of these vials from wardstock was recommended in an external review of our medication system and is now a requirement of the College of Pharmacists of BC.

To facilitate the removal of concentrated KCl vials from wardstock, six additional pre-mixed large volume KCl solutions are now available as floor stock from Stores inventory through Area Supply Service. These are in addition to the four premixed KCl solutions that were previously available (Table 1). All nursing units have now been stocked with the large volume solutions by Area Supply.

**Table 1. Premixed Large Volume KCL Solutions**

KCl 20 mEq in 1L D5W
KCl 40 mEq in 1L D5W*
KCl 20 mEq in 1L 2/3D5W –1/3S
KCl 40 mEq in 1L 2/3D5W –1/3S
KCl 20 mEq in 1L D5W –1/2S
KCl 40 mEq in 1L D5W –1/2S*
KCl 20 mEq in 1L D5S*
KCl 40 mEq in 1L D5S*
KCl 20 mEq in 1L NS*
KCl 40 mEq in 1L NS*

\*New item added to stores inventory

Small volume premixed KCl minibags will also be added to Stores inventory in October for bolus doses (Table 2). These will be stocked by Area Supply on Special and Critical Care areas only based on their estimated utilization. General nursing units will be dispensed KCl minibags (20mEq/100mL) for bolus doses as a personal prescription.

**Table 2. Premixed Small Volume KCl Solutions**

KCl 20mEq in 50mL SWFI*
KCl 20mEq in 100mL SWFI*

\*Only available in sterile water for injection to reduce tonicity

Concentrated KCl vials will remain available as wardstock on all units during the implementation of the premixed solutions. When these vials are ultimately removed, they will be dispensed as a personal prescription for doses not available as a premixed solution.

If you have any questions or concerns regarding this process, please contact Barbara Jewesson or Kenn Koo at 604-875-4077.

### 2. Prescriptions versus Recommendations

The Physician Orders section of the health record is restricted to prescriptions and other patient-care orders. Recommendations or suggestions made by a consulting service should be placed in the progress or consulting notes only. As per current policy, Pharmacists will not process any “suggest” or “recommend” medication orders.

### 3. Ketorolac Injection: Expanded Indications

Ketorolac injection has been approved for short-term management of post-operative pain in patients for whom the oral route is not feasible, and narcotic analgesia or additional narcotic, or a suppository form of a non-steroidal anti-inflammatory drug (NSAID) are not considered desirable.

### 4. Warfarin Brand Selection

Warfarin is now a multi-vendor pharmaceutical product in Canada. While this product was only available through DuPont Pharma (Coumadin<sup>®</sup>) in the past, it is now available through Taro Pharmaceuticals (Taro-warfarin<sup>®</sup>) and Apotex (Apo-warfarin<sup>®</sup>). The Drugs and Therapeutics Committee has recommended that all warfarin brands be considered interchangeable within VHHSC. Pharmaceutical Sciences CSU will continue to carry Coumadin<sup>®</sup> as it remains the most commonly used brand in the community setting and there is no cost advantage for the hospital to switch to another brand. For more information on this issue, please refer to warfarin interchangeability considerations on page 5.

### 5. Revised Drug Administration Policies

**Amiodarone infusions** should be administered using a **0.2 or 0.22 micron in-line filter**. Amiodarone tends to form ultrafine micellar bodies when diluted in IV fluid. These micellar bodies dissociate when the solution is passed through a 0.2 or 0.22 micron filter. Filtering does not affect the potency of the solution.

## *Medication Quality Improvement Committee*

In February 2000, an external reviewer was invited to evaluate the medication distribution system at the VGH site and provide recommendations aimed at further reducing the risk of medication errors in this hospital. While the report acknowledged the multitude of successful policies, procedures and practices that are already in place, recommendations for additional measures were made. These were addressed and endorsed by the Executive Team in June 2000 and responsibility for their potential

implementation was assigned to the appropriate vice-president. Also endorsed was the creation of a Medication Quality Improvement Committee (MQIC), a subcommittee of the Drugs and Therapeutics Committee, whose mandate is "...to improve the prescribing, order processing, dispensing, administering and documenting steps in the medication delivery system to reduce the risk of errors..".

The membership of the MQIC includes co-chairs Pat Semeniuk (Professional Affairs) and Barbara Jewesson (Pharmaceutical Sciences CSU) and representatives from the nursing, medical and pharmaceutical disciplines:

Peter Dawson, PSM, Psychiatry  
Lori Earl, PSM, Internal Medicine  
Sandie Kocher, PSM, Surgery (VGH)  
Mary Lee Johnston, PSM, Surgery (UBCH)  
Leanne Heppell, PSM, Cardiology  
Kathy Weglo, PSC, ICU  
Jo-Ann Ford, CNS, GI & Solid Organ Transplant  
Michael Duchnych, Nurse Educator, BMT  
Khairunnissa Rhemtulla, Nurse Educator, Neurosciences  
Jerry Chen, MD, Vascular Surgery  
Kenn Koo, Sterile Products Supervisor, Pharmaceutical Sciences CSU  
Caryn Pershick, Operations Coordinator, Pharmaceutical Sciences CSU

The focus of the committee over the past year has been to facilitate the implementation of the recommendations from the external review where feasible. These include:

- Removal of concentrated KCl IV vials from wardstock (refer to article on page 2)
- Installation of adequate lighting over the medication carts on VGH nursing units
- Clarification of the practice of nurses summarizing physicians' orders (memo was sent to Patient Services Managers June, 2001)
- Improvement of the medication incident summary reports to facilitate a more meaningful analysis of incidents, especially those involving anticoagulants, analgesics, and insulin

The MQIC will continue to review best practices in medication delivery systems and identify opportunities to reduce the risk of medication errors from occurring in our hospital. If you have any suggestions or comments in this regard, please feel free to forward these to one of the committee members.

## New Drug/Drug Products

### Dipyridamole/ASA Combination (Aggrenox®)

Kerry Wilbur, Pharm.D.

The combination product dipyridamole extended release (ER) plus ASA has been recently added to formulary for the prevention of stroke in patients who have had a previous stroke or transient ischemic attack (TIA).

The antithrombotic action results from additive antiplatelet effects. Aspirin irreversibly inhibits platelet cyclooxygenase, which then inhibits the formation of thromboxane A<sub>2</sub>, a potent vasoconstrictor and inducer of platelet aggregation and platelet-release reaction.

The antiplatelet activity of dipyridamole is less well understood. Dipyridamole reduces platelet aggregation by raising antiplatelet levels of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP).

#### Comparison of Antiplatelet Agents

**Table 1. Comparison of Antiplatelet Drugs**

Drug	Dose	Daily Cost*
EC ASA	81-325mg daily	\$0.01-0.16
Ticlopidine 250mg	250mg bid	\$1.56
Clopidogrel 75mg	75mg daily	\$2.56
ASA 80mg + Dipyridamole 100mg**	40mg (1/2 x 80mg tab) + 200mg bid	\$0.95
ASA 25mg/ Dipyridamole ER 200mg (Aggrenox®)	25mg/200mg bid	\$1.55

EC = enteric coated; ER = extended release  
 \*based on VHHSC acquisition costs  
 \*\*immediate-release dipyridamole, separate entity products

#### Potential Benefits

The Antiplatelet Trialists' Collaboration analysed 14 trials comparing ASA plus dipyridamole with ASA alone for secondary prevention of ischemic events in patients with various vascular diseases (including previous CABG, non-coronary grafting, intermittent claudication, diabetes, and previous

TIA or stroke).<sup>1</sup> They found an overall non-significant 12% reduction in non-fatal stroke in the ASA/dipyridamole groups compared to ASA alone. Since that time, results from the largest randomized study in over 6000 patients evaluating ASA/dipyridamole ER combination have been published. The ESPS-2 trial is the first to demonstrate a significant benefit of ASA/dipyridamole over ASA alone in the prevention of non-fatal stroke in patients with previous TIA or ischemic stroke not receiving ASA or anticoagulant prior to enrolment.<sup>2</sup> The 24-month stroke rates are listed in Table 2.

**Table 2. Comparison of 24-Month Stroke Outcomes from ESPS-2 Trial<sup>3</sup>**

Drug	Total Stroke Rate	Non-fatal Stroke Rate
Placebo	15.8%	13.8%
Dipyridamole 200mg bid	13.2%	11.1%
ASA 25mg bid	12.9%	11.2%
ASA 25mg/ Dipyridamole ER 200mg (Aggrenox®) bid	9.9%*	8.3%*

\*significantly different from placebo, dipyridamole alone, and ASA alone

There was a 23% relative risk reduction with the combination over ASA alone for total strokes and a 25% relative risk reduction for non-fatal strokes (p=0.006). No difference between these two groups were found for other endpoints, including fatal strokes and all-cause mortality.

Putting this data for ASA/dipyridamole into perspective, ASA alone has been shown to reduce the risk of recurrent stroke by 15%-30%.<sup>3,4</sup> Ticlopidine 250mg po bid is associated with a 13% relative risk reduction at 3 years for all strokes when compared to aspirin 650mg po bid (13.8% ASA vs. 11.2% ticlopidine ).<sup>5</sup> However, no difference was found for the primary endpoint of combined stroke or death (22.7% ASA vs. 20% ticlopidine). When compared with ASA 325mg po daily, clopidogrel 75mg po daily demonstrated a 9% relative risk reduction for the combined endpoint of ischemic stroke, myocardial infarction, or vascular death (10.7% ASA vs. 9.8% clopidogrel).<sup>6</sup> However, no difference was found when total stroke was assessed alone (5.3% ASA vs 4.8% clopidogrel), although it is difficult to determine the rate of

recurrent stroke among patients in this study.

### Potential Risks

In the ESPS-2 trial, 15.8% of patients withdrew due to adverse effects from ASA/dipyridamole combination compared with 8.5% of patients receiving ASA alone and 7.7% of patients receiving placebo.<sup>2</sup> The most common adverse effects were headache (39%), dizziness (30%), and gastrointestinal disturbances [e.g. dyspepsia (17.5%) diarrhea (12%), nausea (16%)].

Bleeding of any severity, from any site was similar between the ASA and ASA/dipyridamole groups (8%) and significantly higher compared with placebo (4.5%). Severe or fatal bleeding was also similar between these two groups (1.5%) and non-significantly higher than placebo (0.4%). Bleeding was most commonly reported as epistaxis and hemorrhage not otherwise specified.

### Conclusion

Combination ASA/dipyridamole ER, ticlopidine, and clopidogrel have all been directly compared with aspirin in clinical trials for secondary prevention of ischemic stroke and TIA. There are presently no studies comparing these agents directly with one another. ASA monotherapy remains the least costly first-line therapy for secondary prevention of ischemic stroke or TIA and is recommended by professional bodies such as the American College of Chest Physicians and the American Heart Association. For those patients who have failed ASA therapy, ASA/dipyridamole ER may be considered a therapeutic alternative for ongoing secondary prevention of ischemic stroke or TIA.

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### Warfarin Interchangeability Considerations

Anne Sawoniak B. Sc. (Pharm), Reviewed by Karen Shalansky, Pharm.D., Rubina Sunderji, Pharm.D., Peter Zed, Pharm.D.

For years Dupont Pharma manufactured the only warfarin product (Coumadin<sup>®</sup>) marketed in Canada. Recently, two additional warfarin products have received approval in Canada. These products are Taro-warfarin<sup>®</sup> (Taro Pharmaceuticals) and Apo-warfarin<sup>®</sup> (Apotex).

Warfarin is a narrow therapeutic index drug with nonlinear pharmacodynamics that requires close therapeutic monitoring to provide optimal antithrombotic effect with minimal bleeding complications. Because minor dose changes can result in clinically significant changes in INR response, the issue of equivalence between brand name and generic warfarins requires careful evaluation.<sup>1</sup> Table 1 compares several parameters for determining equivalence between the various warfarin formulations in Canada.

**Table 1. Comparison of Warfarin Formulations**

Manufacturer	Dupont Pharma	Taro	Apotex
Content Uniformity	92.5-107.5% of labeled strength	Follows Dupont specifications	85-115% of labeled strength
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/tablet			
1mg strength	\$0.10*	\$0.20	\$0.20
5mg strength	\$0.08*	\$0.17	\$0.17

\*VHHC acquisition costs (costs in the community may be higher)

### Content Uniformity

Single tablets are assayed to determine the amount of active ingredient; this amount is then compared to the labeled strength and the content uniformity is determined. Stringent content uniformity assures consistency of tablet strength within and amongst batches of warfarin.

The United States Pharmacopoeia (USP) specifies that 10 tablets from any batch must contain 85-115% of labeled strength with a standard deviation (SD) of <6%. If one tablet falls outside this range, then 20 more tablets must be tested. Of these 30 tablets, SD must be <7.8% and all tablets must be within 75-125% with only 1 tablet allowed <85% or >115%.<sup>2</sup> Apotex follows USP specifications<sup>3</sup>. Dupont Pharma and Taro use more stringent tablet uniformity specifications than those designated by USP.<sup>4,5</sup> Initial 10 tablets tested must contain 92.5-107.5% of labeled strength. Standard deviation must be <3%. If 1 tablet falls outside this range, then 20 more tablets must be tested. Of these 30 tablets, SD must be <3.9% and all tablets must be within 87.5-112.5% with only 1 tablet allowed <92.5% or >107.5%.<sup>6</sup>

#### *Mean Bioequivalence*

To establish bioequivalence in a narrow therapeutic index drug, a test drug must meet certain bioequivalence standards when compared to the reference drug. Health Canada has developed a set of standards that are used to determine bioequivalence in Canada: a 95% confidence interval of the pharmacokinetic parameters of area-under-the-curve and peak serum concentration of the test drug must be within 80-125% of the value of the reference drug in healthy subjects, in both fed and fasting states.<sup>7</sup> Both Taro-warfarin<sup>®</sup> and Apo-warfarin<sup>®</sup> meet these Health Canada requirements.<sup>3,4</sup>

#### *Individual Bioequivalence*

Because drug pharmacokinetics among individual patients are variable, 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 and involved a comparison of Taro-warfarin<sup>®</sup> against the Coumadin<sup>®</sup> brand in 23 patients. This study confirmed findings from previous mean bioequivalence studies that Taro-warfarin<sup>®</sup> and Coumadin<sup>®</sup> appear to be equivalent in terms of their pharmacokinetic parameters.<sup>8</sup>

#### *Therapeutic Equivalence*

Therapeutic equivalence of warfarin products is

assessed by a comparison of INR values in crossover studies in patients taking chronic warfarin therapy. These studies are the only means to test therapeutic outcomes of switching warfarin products; other parameters mentioned thus far measure only pharmacokinetic or surrogate markers of warfarin product equivalence. Therapeutic equivalence studies have not been performed with the Taro or Apotex products. Three studies involving about 400 patients have been conducted with an American generic formulation - Barr-warfarin<sup>®</sup>.<sup>9-11</sup> Two studies<sup>9,10</sup> were observer-blinded, randomized, crossover designs and one study<sup>11</sup> was an open-label, non-randomized design. All three studies demonstrated efficacy and safety with Barr-warfarin<sup>®</sup> compared to Coumadin<sup>®</sup>. Bleeding complications were not statistically different between the two products. As well, dosage adjustments were required no more frequently with the Barr product compared to Coumadin<sup>®</sup>. These results suggest that extra INR monitoring is unnecessary when patients are switched from Coumadin<sup>®</sup> to the Barr formulation.<sup>9-</sup>

<sup>11</sup> However, there have been published case reports of subtherapeutic INRs associated with switching from Coumadin<sup>®</sup> to Barr-warfarin<sup>®</sup>.<sup>4</sup>

#### *Cost and Unit Dose Packaging*

Refer to Table 1 for cost comparisons. Dupont Pharma offers unit dose packaging for their product; neither Taro nor Apotex offer this packaging option as yet.

#### *Conclusions*

While Taro and Dupont Pharma appear to follow stringent content uniformity and bioequivalence guidelines, no therapeutic equivalence studies have been published for these products. Such studies would clarify the need for supplementary INR monitoring when switching between brands. However, where close monitoring of INR and clinical status is to be expected in the hospital setting, brand to brand switches should not pose as a therapeutic issue. Accordingly, the Drugs and Therapeutics Committee has deemed that all warfarin brands be considered interchangeable at VHHSC. Dupont Coumadin<sup>®</sup> will be retained on formulary since the majority of patients are still receiving this preparation, it has unique unit dose packaging and there is no cost advantage of changing to another brand. Close INR monitoring is recommended post-discharge, especially if an alternate brand is resumed.

*References available upon request.*

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