

Pharmacy Newsletter

A Publication of Highline Medical Center Pharmacy

Administration of Vitamin K for INR Reversal

by Cathie Jamieson, RPh, BS Pharm, MA

On September 15, 2009, the Highline Medical Center Pharmacy and Therapeutics Committee approved a vitamin K administration protocol for INR reversal based on the 2008 Chest Guidelines.¹ These guidelines recommend the administration of vitamin K via the oral route for INRs greater than 5 in the presence of no significant bleeding. For serious bleeding, at any elevation of INR, or life-threatening bleeding, intravenous (IV) administration of vitamin K is recommended.

Routes of administration of vitamin K include oral, IV, and subcutaneous (subcut). Kinetics of the different routes of administration are compared in Table 1 (retrieved from <http://www.merck.com/mmpe/lexicomp/phytonadione.html>, September 24, 2009).

Oral administration of vitamin K is predictably effective, safe, and more convenient when compared to the parenteral administration of the medication. Unlike the intravenous route, it carries a low risk of hypersensitivity or anaphylaxis.² The intravenous route is purported to give the most predictable response.² Concerns

over severe hypersensitivity reactions and hypotension have restricted the route to patients with life-threatening bleeding, INRs above 20, or in patients who are unable to tolerate the oral route of administration.

The response to vitamin K administered subcutaneously may be delayed and unpredictable.³ A meta-analysis of 10 randomized and 11 prospective trials was performed to determine the relative effectiveness of the various routes of Vitamin K administration.⁴ The results are shown in Table 2.

Table 2: Percent of patients with an INR between 1.8 to 4, 24 hours after stopping warfarin and administration of Vitamin K

Route	Percent	CI (%)
Placebo	20	95
Oral	82	95
IV	77	95
Subcut	31	95

Table 1: Pharmacokinetics

	Onset of Action	Peak Effect	Absorption	Metabolism	Excretion
Oral	6-10 hours	28-48 hours	Intestinal in presence of bile	Hepatic	Urine and Feces
IV	1-2 hours	12-14 hours		Hepatic	Urine and Feces
Subcut	Variable	Variable	Variable	Hepatic	Urine and Feces

(Continued on page 2)

SEPT/OCT 2009

Volume 30 • Issue 4

INSIDE THIS ISSUE

PAGE 2: Plavix® and PPIs

PAGE 4: Study Review

PAGE 6: FDA Updates

PAGE 8: Therapeutics Committee Update

Vitamin K - *Continued from front page*

The subcutaneous route for vitamin K administration appears to be no better for this purpose than placebo concluded the authors and should not be employed.

The oral route is the preferred route since it was concluded that the oral and intravenous routes were equally efficacious.⁴ Effective doses ranged from 1 to 2.5 and 0.5 to 3 mg for the oral and intravenous routes, respectively.⁵ Per the Highline Medical Center's protocol, vitamin K will be diluted in D5W or NS 50mL and infused over 30 minutes for IV administration to reduce the potential of hypotension, hypersensitivity or anaphylactic reactions.

References:

1. Ansel J, Hirsh J, Hylek E, Jacobson A, Crowther M, and Palareti G. Pharmacology and management of the vitamin K antagonists, *Chest* 2008; 133:160S-198S.
2. Hirsh J, Dalen JE, Anderson DR, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest* 1998; 114:445S-69.
3. Whitling AM, Bussey HI, Lyons RM. Comparing different routes and doses of phytonadione for reversing excessive anticoagulation. *Arch Intern Med* 1998; 158:2136-40.
4. Dezee KJ, Shimeall WT, Douglas KM, Shumway NM, O'Malley PG Treatment of excessive anticoagulation with phytonadione (vitamin K): a meta-analysis. *Arch Intern Med*. 2006 Feb 27; 166(4): 391-7.
5. Crowther MA, Douketis JD, Schnurr T, Steidl L, Mera V, Ultori C, Venco A, Ageno W. Oral vitamin K lowers the international normalized ratio more rapidly than subcutaneous vitamin K in the treatment of warfarin-associated coagulopathy. A randomized, controlled trial. *Ann Intern Med* 2002 Aug 20; 137(4): 251-4.

Plavix[®] and PPIs: Should They Be Used Together?

by Erin Cutter, University of Washington Pharmacy Extern

Introduction

Clopidogrel (Plavix[®]) and other anti-platelet agents are frequently prescribed for reduction of atherosclerotic events following recent myocardial infarction (MI), peripheral artery disease, and acute coronary syndrome, and for the secondary prevention of non-cardioembolic stroke. Depending on the indication, it may be used alone or in combination with aspirin or warfarin for patients with a higher risk of atherothrombotic events.

Due to an increased risk of gastric ulcers and GI bleeding with the dual anti-platelet therapy of aspirin and clopidogrel, the American College of Cardiologists, the American Heart Association, and the American College of Gastroenterology recommend additional administration of a proton pump inhibitor (PPI). For this reason, PPIs are often prescribed in combination with clopidogrel. Concern that this drug combination may not be the best option for patients is due to the potential drug interaction between PPIs and clopidogrel.

Clopidogrel¹

Clopidogrel is a thienopyridine prodrug that undergoes hepatic activation in a two-step process by several cytochrome P450

enzymes; CYP2C19 is the major enzyme responsible for its activation. The active metabolite of clopidogrel binds and irreversibly inhibits the P2Y₁₂ platelet receptor, inhibiting adenosine diphosphate (ADP)-mediated platelet activation and aggregation, and promotes prevention of clot formation, which could lead to stroke or heart attacks.

Proton Pump Inhibitors^{1,2}

Proton pump inhibitors suppress hydrogen ion secretion in the gastric lumen by inhibiting H⁺/K⁺ ATPase, the proton pump responsible for the terminal step in gastric acid secretion. In the liver, PPIs are metabolized by the CYP450 enzymes 2C19 and 3A4. In addition, some PPIs have been shown to inhibit CYP 2C19, primarily omeprazole and lansoprazole with omeprazole having a 10 fold higher affinity for the CYP 2C19 isoenzyme compared to CYP 3A4. Lansoprazole has been shown to inhibit CYP 2C19 in vitro; however, in vivo data show no significant inhibition of the CYP 2C19 enzyme. Pantoprazole and rabeprazole have not shown any significant drug interactions when administered in combination with other CYP 2C19 substrates including: warfarin, theophylline, phenytoin, and tacrolimus.

Platelet Studies^{3,4,5}

In 2008, the Omeprazole Clopidogrel Aspirin study³ showed that concomitant use of omeprazole and clopidogrel significantly decreased the anti-platelet effects of clopidogrel in patients receiving both aspirin and clopidogrel. Investigators hypothesized that a potential drug-drug interaction at the 2C19 enzyme was responsible for the reduction in anti-platelet activity normally provided by clopidogrel. This sparked concern that other PPIs could have a similar effect on clopidogrel activity. Since PPIs differ in their metabolism effects, additional studies were conducted to assess whether the drug-drug-interaction between omeprazole and clopidogrel is a class effect.

In January of 2009 investigators published a study that analyzed the effects of esomeprazole and pantoprazole on the anti-platelet activity of clopidogrel in 300 patients receiving both aspirin and clopidogrel.⁴ The authors found that administration of pantoprazole or esomeprazole with clopidogrel did not affect vasodilator-stimulated phosphoprotein (VASP), an assay used to evaluate platelet function in response to clopidogrel, or ADP-induced platelet aggregation compared with patients not receiving additional PPI therapy. Another similar study comparing the effects of PPI use with concomitant dual anti-platelet therapy published in March 2009 found that ADP-induced platelet aggregation was significantly higher in patients taking omeprazole compared to patients without PPI treatment, and those taking either pantoprazole or esomeprazole.⁵

Population Studies^{6,7,8}

Canadian investigators conducted a study in 13,000 patients receiving clopidogrel and taking a PPI to determine if concomitant use of PPIs and clopidogrel lead to a greater risk of adverse cardiac events within 90 days of therapy initiation.⁶ Concurrent use of PPIs was found to be associated with a 27% increase risk of re-infarction. Stratified analysis of the type of PPI used indicated that pantoprazole was not associated with recurrent MI among patients receiving clopidogrel. In contrast, compared with no treatment, other PPIs were associated with a 40% increase risk of recurrent MI. The investigators concluded that the reduction in the anti-platelet effects of clopidogrel by PPIs was not a class effect and that potential drug interactions might be avoided by using pantoprazole.

In another recently published study by Ho, et al., investigators found that patients taking both clopidogrel and a PPI had a 25% increased risk of dying or being re-hospitalized for a cardiac issue.⁷ When examining individual PPIs, they noted a consistent association between omeprazole and rabeprazole and an increased risk of death or rehospitalization. Association with pantoprazole could not be explored due to a small sample size.

Of note, subgroup analysis in both of these population-based studies has revealed significant differences in the rates of comorbidities between patients taking a PPI and those without PPI treatment. In fact, patients taking PPIs had higher rates of diabetes mellitus, chronic obstructive pulmonary disease, renal disease, peripheral vascular disease, and previous heart conditions. As such, the increased risk of bleeding associated with concomitant use of clopidogrel and PPIs may be a spurious correlation if patients who take PPIs are generally sicker than those patients not on PPI therapy. Post hoc analysis of the Clopidogrel for the Reduction of Events During Observation has indicate patients taking PPIs are at increased risk of cardiovascular events with or without concomitant clopidogrel use.

Pharmacogenetic Influence⁹

Pharmacogenetic studies have shown that individuals express different levels of CYP enzymes based on their genetic profile; CYP2C19 is known to have 8 variant alleles that can significantly alter enzyme activity. The polymorphism of CYP2C19 can be classified into 3 distinct groups: rapid metabolizers, intermediate metabolizers and slow metabolizers. This genetic variability has been shown to have clinical consequences for both clopidogrel and PPI. Theoretically, poor metabolizers are at a higher risk of adverse events due to the PPI/clopidogrel drug-drug-interaction since coadministration of PPIs may further decrease metabolism of clopidogrel to its active metabolite resulting in less platelet inhibition.

Recommendations¹⁰

Based on current research, the potential interaction between clopidogrel and PPIs is most convincing for omeprazole. The true mechanism of the interaction is uncertain though it is most likely due to competitive inhibition of the CPY 2C19 isoenzyme. The effects of other PPIs on clopidogrel's anti-platelet activity are unclear, though pantoprazole seems to have the least influence on CYP 2C19 and on the activity of clopidogrel based on both pharmacodynamic and clinical evidence. Omeprazole is the only PPI to be clinically evaluated for this drug interaction in a randomized controlled trial and thus further research is needed to compare the pharmacokinetic and pharmacodynamic effects as well as clinical outcomes of the individual PPIs on clopidogrel in randomized controlled trials to determine a causal relationship between clopidogrel, the PPIs, and increased adverse events.

In the meantime, the FDA recommends that providers continue to prescribe clopidogrel as it has proven benefits in secondary prevention of stroke and heart attack. However, healthcare providers should assess the requirement for concomitant PPI use in patients taking clopidogrel and to caution patients against using OTC PPIs, including Prilosec®. Additionally,

H2 receptor antagonists, such as ranitidine, are an acceptable alternative to PPIs for management of GERD. Nonetheless, if a patient has indications for administration of both clopidogrel and a PPI, pantoprazole should be the PPI of choice since it is the least likely PPI to interact with clopidogrel.

References

1. Kahlique SC and Cheng-Lai A. Drug interaction between Clopidogrel and proton pump inhibitors. *Cardiol Rev* 2009;17(4):198-200.
2. Blume H, Donath F, Warnke A, Schug BS. Pharmacokinetic drug interaction profiles of proton pump inhibitors. *Drug Saf.* 2006; 29:769-784
3. Gilard M, Arnaud B, Cornily J, et al. Influence of omeprazole on the anti-platelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA study. *J Am CollCardiol.* 2008 Jan 22;51(3):256-60
4. Siller-Matula JM, Spiel Ao, Lang IM, et al. Effects of pantoprazole and esomeprazole on platelet inhibition by clopidogrel. *Am Heart Journal.* 2009; 157:148.
5. Sibbing D, Morath T, Stegherr J, et al. Impact of proton pump inhibitors on the anti-platelet effects of clopidogrel. *ThrombHaemost*2009; 101:714-719.
6. Juurlink DN, Gomes , Ko DT, et al. A population based study of the drug interaction between proton pump inhibitors and clopidogrel. *CMAJ.* 2009;180(7)
7. Ho M, Maddox TM, Wang L, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA.* 2009;301:937-944.
8. Dunn SP, Macaulay TE, Brennan DM et al. Baseline protonpump inhibitor use is associated with increased cardiovascular events with and without use of clopidogrel in the CREDO trial. *Circulation.* 2008; 118:S_815:abstract 3999.
9. Norgard NB, Mathews KD, Wall GC. Drug-drug interaction between clopidogrel and the proton pump inhibitors. *AnnlsPharmacotherapy.*2009
10. Food and Drug Administration. "Early Communication about an ongoing Safety Review of clopidogrel bisulfate." [fda.gov \(clopidogrel\)](http://fda.gov/clopidogrel) Accessed July 2009.

After this article was written, the investigators of the Clopidogrel and the optimization of Gastrointestinal Events (COGENT-1) trial presented preliminary data from their randomized, double-blind, interventional trial exploring the use of a combination clopidogrel-omeprazole pill with daily aspirin to dual anti-platelet therapy without a PPI. Investigators found no significant difference in the rate of major cardiac adverse events with the anti-platelet/PPI combination compared to therapy without a PPI. These data suggest that there may not be need for concern when combining PPIs and the dual anti-platelet therapy of aspirin and clopidogrel. However, further research is needed to confer these results and caution should still be used when prescribing any PPI and clopidogrel.

Bhatt D. The COGENT trial. Presented at the 21st annual Transcatheter Cardiovascular Therapeutics scientific symposium; September 24, 2009; San Francisco, CA.

Study Review

by Rebecca Kingsley, Pharm D

A large, prospective study published in 2009 examined the incidence of major hemorrhage and thromboembolism among patients treated with oral anticoagulants (vitamin K antagonists like warfarin) for mechanical heart valve prostheses, atrial fibrillation (a. fib) or history of myocardial infarction (MI) in 4202 patients in the Netherlands to assess the optimal international normalized ratio (INR) goal by calculating INR-specific incidence rates.¹ Patients were included if they were treated with vitamin K antagonists in the Leiden Anticoagulation

Clinic during the period of 1994 to 1998 for one of the above indications.

International normalized ratio goal ranges were 3.6-4.8 for mechanical heart valve prosthesis and 3-4.5 for MI and a. fib at the start of the study; these goals changed in 1996 to an INR goal range of 3-4 for mechanical heart valve prosthesis or MI and 2.5-3.5 for a. fib. Major hemorrhage was defined as intracranial, spinal, and extracranial bleeding events. Major throm-

boembolism was defined as ischemic stroke, myocardial infarction and peripheral thromboembolism. The optimal INR goal ranges with the least adverse events were found to be 2.5-2.9, 3-3.4, and 3.5-3.9, for mechanical heart valve replacement, a. fib and MI, respectively. For these ranges the combined incidence rates, thrombotic and hemorrhagic, were 2 events per 100 person-years (95% CI, 0.2-5.7), 2.4 events per 100 person-years (95% CI, 1.5-3.5), and 1.1 events per 100 person-years (95% CI, 0.5-1.9), for mechanical heart valve prostheses, a. fib and MI, respectively. Hemorrhagic rates increased with higher INRs and thrombotic rates increased with lower INRs (see table).

The investigators concluded that these optimal target INRs may be required to reduce thrombotic and hemorrhagic adverse events, however they also stressed that further studies must be conducted to determine if this is true. This study did not examine individual patient characteristics, which may require individualizing the goal range for unique patients who are at greater risk for bleeding or clotting. The authors did however use actual INR levels that the clinic achieved rather than just goals. Also important to note is that combination therapy of vitamin K antagonists and antiplatelet drugs was not common in this patient population. This is an important study, which may help to improve patient outcomes, but further studies need to be conducted to determine the validity of the results, especially in our patient population where patients do tend to take antiplatelet medications in addition to vitamin K antagonists.

Currently we depend on the Chest Guidelines² to determine the standard of care for patients taking warfarin: mechanical heart valve prosthesis INR goal = 2.5-3.5, a. fib and MI INR goal = 2-3. Until the Chest Guidelines support changing the recommended goal ranges, the findings in this study should only be viewed as educational.

Reference:

1. Torn M, Cannegieter SC, Bollen WLEM, van der Meer FJM, van der Wal EE, Rosendaal FR. Optimal level of oral anticoagulant therapy for the prevention of arterial thrombosis in patients with mechanical heart valve prostheses, atrial fibrillation or myocardial infarction. Arch Intern Med 2009;169(13):1203-1209.
2. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists. Chest 2008;133:160S-198S. Available at: http://www.chestjournal.org/content/133/6_suppl/160S.full.html

Incidence rates of untoward events according to severity¹

INR	All Events Incidence ^a (95% CI)	Life-Threatening and Fatal Events Incidence ^a (95% CI)
Mechanical heart valve		
<2.0	31.9 (5.7-79.4)	10.6 (0.0-42.6)
2.0-2.4	6.7 (0.6-19.4)	3.3 (0.0-13.3)
2.5-2.9	2.0 (.02-5.7)	1.0 (0.0-13.3)
3.0-3.9	2.5 (1.3-4.0)	1.1 (0.4-2.1)
4.0-4.9	3.3 (1.6-5.5)	1.8 (0.6-13.2)
≥5.0	24.7 (13.3-39.7)	5.3 (0.9-13.2)
Atrial fibrillation		
<2.0	14.0 (6.8-23.7)	7.6 (2.7-15.1)
2.0-2.9	2.7 (1.7-3.9)	0.6 (0.2-1.2)
3.0-3.4	2.4 (1.5-3.5)	1.0 (0.5-1.8)
3.5-3.9	2.6 (1.6-3.9)	1.0 (0.4-1.9)
4.0-4.9	4.7 (3.0-6.8)	1.4 (0.5-2.6)
≥5	42.3 (29.2-57.8)	15.7 (8.2-25.6)
Myocardial infraction		
<2.0	7.7 (1.4-19.1)	5.1 (0.4-14.9)
2.0-2.9	2.5 (1.3-4.1)	1.7 (0.7-3.0)
3.0-3.4	1.6 (0.9-2.6)	0.7 (0.2-1.3)
3.5-3.9	1.1 (0.5-1.9)	0.6 (0.2-1.2)
4.0-4.9	3.1 (3.1-6.5)	2.5 (1.4-4.0)
≥5	27.8 (27.8-55.0)	12.7 (6.2-21.4)

Abbreviations: CI, confidence interval; INR, international ratio.
^aPer 100 patient-years

FDA Updates

Promethazine Hydrochloride Injection

FDA notified healthcare professionals that a Boxed Warning is being added to the prescribing information for Promethazine Hydrochloride products, describing the risks of severe tissue injury, including gangrene, requiring amputation following intravenous administration of promethazine. The Boxed Warning will remind practitioners that due to the risks of intravenous injection, the preferred route of administration is deep intramuscular injection and that subcutaneous injection is contraindicated.

Perivascular extravasation, unintentional intra-arterial injection and intraneuronal or perineuronal infiltration of the drug may result in irritation and tissue damage. Healthcare professionals should be alert for signs and symptoms of potential tissue injury including burning or pain at the site of injection, phlebitis, swelling, and blistering.

[09/16/2009 - Information for Healthcare Professionals - FDA]

[09/16/2009 - News Release - FDA]

Natalizumab (marketed as Tysabri)

FDA continues to receive reports of progressive multifocal leukoencephalopathy (PML) in patients receiving Tysabri. Tysabri was approved by the FDA for the treatment of relapsing forms of multiple sclerosis (MS) in November 2004 and for moderately to severely active Crohn's disease in January 2008. From July 2006, (when Tysabri marketing resumed) to September 8, 2009, 13 reported cases of Tysabri-related PML were confirmed worldwide in patients being treated for MS with Tysabri monotherapy. There have been no postmarketing reports of PML in patients treated with Tysabri for Crohn's disease. Less than 2% of Tysabri use in the U.S. has been in patients with Crohn's disease. Based on available data from the U.S. and outside of the U.S., the current rate of PML in patients who have received at least 24 infusions ranges from 0.4 to 1.3 per 1,000 patients.

The risk for developing PML appears to increase with the number of Tysabri infusions received. At this time, the FDA is not requiring changes regarding PML to the Tysabri prescribing information or to the Tysabri risk management plan, called the TOUCH Prescribing Program.

[09/16/2009 - Information For Healthcare Professionals - FDA]

Myfortic (mycophenolic acid)

Novartis and FDA notified healthcare professionals that

cases of Pure Red Cell Aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil (MMF) in combination with other immunosuppressive agents. MMF is metabolized to mycophenolic acid (MPA), the active ingredient in Myfortic and the active form of the drug. The WARNINGS and ADVERSE REACTIONS sections of the Myfortic Prescribing Information have been revised to reflect this new safety information.

PRCA is a type of anemia in which there is a selective reduction of red blood cell precursors on bone marrow examination. Patients with PRCA may present with fatigue, lethargy, and/or abnormal paleness of the skin (pallor). In some cases, PRCA was found to be reversible with dose reduction or cessation of MMF therapy. In transplant patients, however, reduced immunosuppression may place the graft at risk.

[09/03/2009 - Dear Healthcare Professional Letter - Novartis]

[07/10/2009 - Prescribing Information and Medication Guide - Novartis]

CellCept (mycophenolate mofetil) August 2009

Roche notified healthcare professionals that cases of Pure Red Cell Aplasia (PRCA) have been reported in patients treated with CellCept. The WARNINGS and ADVERSE REACTIONS sections of the CellCept Prescribing Information have been revised to reflect this new safety information.

PRCA is a type of anemia in which there is a selective reduction of red blood cell precursors on bone marrow examination. Patients with PRCA may present with fatigue, lethargy, and/or abnormal paleness of the skin (pallor). In some cases, PRCA was found to be reversible with dose reduction or cessation of CellCept therapy. In transplant patients, however, reduced immunosuppression may place the graft at risk.

[08/14/2009 - Dear Healthcare Professional Letter - Roche]

[06/18/2009 - Prescribing Information and Medication Guide - Roche]

Leukotriene Inhibitors: Montelukast (marketed as Singulair), Zafirlukast (marketed as Accolate), and Zileuton (marketed as Zyflo and Zyflo CR)

The June 12, 2009 Healthcare Professional Sheet has been updated. FDA provided healthcare professionals with updated information on the original March 2008 early communication and January 2009 follow-up communication about the ongoing

safety review for the leukotriene inhibitors, montelukast, zafirlukast and zileuton. Neuropsychiatric events have been reported in some patients taking montelukast (Singulair), zafirlukast (Accolate), and zileuton (Zyflo and Zyflo CR). FDA has requested that manufacturers include a precaution in the drug prescribing information (drug labeling). The reported neuropsychiatric events include postmarket cases of agitation, aggression, anxiousness, dream abnormalities and hallucinations, depression, insomnia, irritability, restlessness, suicidal thinking and behavior (including suicide), and tremor. FDA recommends that:

- Patients and healthcare professionals should be aware of the potential for neuropsychiatric events with these medications.
- Patients should talk with their healthcare providers if these events occur.
- Healthcare professionals should consider discontinuing these medications if patients develop neuropsychiatric symptoms.

[06/12/2009, Updated 08/28/2009 - Healthcare Professional Sheet - FDA]

Intelence (etravirine)

Tibotec Therapeutics and FDA notified healthcare professionals of revisions to the WARNINGS AND PRECAUTIONS section of the prescribing information for Intelence (etravirine). There have been postmarketing reports of cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme, as well as hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure. Intelence therapy should be immediately discontinued when signs and symptoms of severe skin or hypersensitivity reactions develop.

[August 2009 - Dear Healthcare Professional Letter - Tibotec Therapeutics]

Tumor Necrosis Factor (TNF) Blockers (marketed as Remicade, Enbrel, Humira, Cimzia, and Simponi) August 2009

FDA notified healthcare professionals that it has completed its analysis of tumor necrosis factor (TNF) blockers and has concluded that there is an increased risk of lymphoma and other cancers associated with the use of these drugs in children and adolescents. This new safety information is now being added to the Boxed Warning for these products. FDA has also identified new safety information related to the occurrence of leukemia and new-onset psoriasis in patients treated with TNF blockers. The current prescribing information for TNF blockers does contain a warning for malignancies, but does not specifically mention leukemia. FDA is also requiring updates to the current

Medication Guide to help patients understand the risks associated with TNF blocker therapy.

TNF blockers are approved for the treatment of one or more of a number of immune system diseases including juvenile idiopathic arthritis (JIA), rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, Crohn's disease, and ankylosing spondylitis.

[08/28/2009 - Q&As - FDA]

[08/04/2009 - Information for Healthcare Professionals - FDA]

[08/04/2009 - Follow-up to Early Communication about the Ongoing Safety Review of Tumor Necrosis Factor (TNF) Blockers - FDA]

Varenicline (marketed as Chantix) and Bupropion (marketed as Zyban, Wellbutrin, and generics)

FDA notified healthcare professionals and patients that it has required the manufacturers of the smoking cessation aids varenicline (Chantix) and bupropion (Zyban and generics) to add new Boxed Warnings and develop patient Medication Guides highlighting the risk of serious neuropsychiatric symptoms in patients using these products. These symptoms include changes in behavior, hostility, agitation, depressed mood, suicidal thoughts and behavior, and attempted suicide. The added warnings are based on the continued review of postmarketing adverse event reports for varenicline and bupropion received by the FDA. These reports included those with a temporal relationship between the use of varenicline or bupropion and suicidal events and the occurrence of suicidal ideation and suicidal behavior in patients with no history of psychiatric disease.

Healthcare professionals should advise patients to stop taking varenicline or bupropion and contact a healthcare provider immediately if they experience agitation, depressed mood, and any changes in behavior that are not typical of nicotine withdrawal, or if they experience suicidal thoughts or behavior.

[07/01/2009 - Public Health Advisory - FDA]

[07/01/2009 - Information for Healthcare Professionals - FDA]

[07/01/2009 - News Release - FDA]

Highline Medical Center's Pharmacy and Therapeutics Committee Update

Formulary Additions/Deletions

Addition: Doripenem (Doribax®)- Antimicrobial

Deletion: Imipenem (Primaxin®)- Antimicrobial

Doripenem has been added to Highline Medical Center's hospital formulary as the primary carbapenem. It has activities against gram-positive, gram-negative, and anaerobes. Uses include the treatment of complicated intra-abdominal infections and complicated urinary tract infections, including pyelonephritis. Recent studies have shown that hospital LOS and time on mechanical ventilation were significantly shorter with doripenem compared to imipenem. Doripenem potency is comparable to those of meropenem and imipenem against gram-positive cocci. Current daily expense for doripenem 500mg q8h would be \$70.38 per day versus imipenem 500mg IV q6h at \$83 per day. Converting to doripenem as the primary carbapenem would save the organization approximately \$29,000 per year (based on the financial impact model provided by Ortho-McNeil).

The following therapeutic interchange was approved:

Drug/Dose	Therapeutic Interchange	Renal Dosing	
	CrCl > 50 mL/min	CrCl 30-50 mL/min	CrCl 11-29 mL/min
Imipenem (Primaxin®) 1000mg q8h	Doripenem 500 mg q8h	Initial dose 500mg then, 250mg q8h	Initial dose 500 mg then, 250 mg q12h
Imipenem (Primaxin®) 1000mg q8h			
Imipenem (Primaxin®) 1000mg q8h			
Imipenem (Primaxin®) 1000mg q8h			
Imipenem (Primaxin®) 1000mg q8h			
Higher doses may be required for more resistant bacterial species, especially in morbidly obese patients with normal GFR. If greater than 125kg, contact physician/infectious disease physician for consultation			

Addition: Prasugrel (Effient®)- Antiplatelet

Prasugrel is a pro-drug that is converted to an active metabolite via Phase I liver metabolism (CYP450 reaction). It is a thienopyridine adenosine diphosphate receptor antagonist that irreversibly inhibits platelet activation and aggregation.

Its therapeutic indication is to reduce the rate of thrombotic cardiovascular (including stent thrombosis) events in patients with unstable angina, non-ST-segment myocardial infarction (NSTEMI), or ST-elevation MI (STEMI) managed with percutaneous coronary intervention (PCI). The most significant adverse event noted is the increased risk of bleeding with other side effects similar to clopidogrel. The recommended dosing is one loading dose of 60mg followed by 10mg per day.

Prior to initiating therapy, adequate screening must be conducted to avoid treating patients who are at increased risk of bleeding (see Black Box Warning below). Recommended monitoring parameters include checking hemoglobin and hematocrit periodically.

Black Box Warnings:

- **May cause significant or fatal bleeding.** Use is contraindicated in patients with history of TIA or stroke or active bleeding. Additional risk factors for bleeding include:
 - Body weight <60kg
 - Propensity to bleed
 - Concomitant use of medications that increase the risk of bleeding (e.g., warfarin, heparin, fibrinolytic therapy, chronic use of NSAIDs).
- **In patients ≥75 years of age, use is not recommended due to increased risk of fatal and intracranial bleeding and uncertain benefit;** use may be considered in high-risk situations (e.g., patients with diabetes or history of MI).
- **Discontinue ≥7 days prior to coronary artery bypass graft (CABG) surgery; increased risk of bleeding; do not initiate therapy in patients likely to undergo CABG.**

If you have any questions, please contact Cathie Jamieson at 206-988-5787.