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GENETIC TESTING AND WARFARIN DOSING

DNA, genes, and the ability to analyze these elements through lab testing has moved to the forefront of medicine. Genetic testing has diverse applications in medicine, many of which are life-saving. Testing to optimize drug therapy has been applied, most notably, to the blood thinner warfarin; however, cost effectiveness remains questionable at this time.

The optimal induction dose of warfarin varies from person to person such that the medication remains the second most common drug implicated in emergency room visits for adverse drug events.¹ One third of population variance in warfarin dosing can be explained by two genes: Cytochrome P450 2C9 and Vitamin K Epoxidase Reductase (VKORC1).²

These two genes assess an individual patient's sensitivity to warfarin and his/her rate of warfarin metabolism. Rationale for the use of genetic testing includes a reduction in time to therapeutic INR, accelerated achievement of stable anticoagulation, and a decrease in risk for major hemorrhage during the first month of therapy.

However, cost effectiveness, when compared to current empirical induction therapy, remains a key limitation to genetic testing due to



increased cost (\$200-\$500 per test), limited availability, and waiting period/delay in therapy while testing is conducted. In addition, reliance in genetic testing dose predictions without follow-up INR monitoring could result in poorer clinical outcomes compared to empirical induction therapy.

Genetic testing provides an additional clinical measure to initiate a starting dose of warfarin; however, the degree to which genetic testing decreases rates of bleeding remains unclear. Despite the use of genetic testing, variability in dosing remains and prospective studies to analyze the true benefit over empirical therapy is needed.

While the FDA label states that genetic information should be considered in deciding an induction warfarin dose, clearly, more research is needed before such testing is recommended on a routine basis.

Source: FDA Information Update for Health Professionals (more at <http://www.fda.gov>)

BRAND (GENERIC) DRUG	RECENT UPDATES / ALERTS ON SELECTED DRUGS
<p>Uloric® (febuxostat)</p>	<p><u>New Drug Approval for Chronic Management of Gout (posted 2/20/2009)</u></p> <p>Takeda received U.S. Food and Drug Administration approval for Uloric (febuxostat), the first new drug to be approved for gout in over 40 years. Uloric is a nonpurine, selective inhibitor of xanthine oxidase and has a completely different structure from allopurinol (Zyloprim).</p> <p>http://www.fda.gov/cder/rdmt/NME_ApprovalsCY09.pdf</p>
<p>Zonegran® (zonisamide)</p>	<p><u>Zonisamide Metabolic Acidosis Risk (posted 2/23/2009)</u></p> <p>The U.S. Food and Drug Administration issued an alert to health care professionals that treatment with zonisamide can cause metabolic acidosis. Zonisamide, an antiepileptic drug approved as adjunctive therapy for the treatment of partial seizures in adults with epilepsy, appears to cause metabolic acidosis more frequently and severe in younger patients and patients with predisposing conditions or therapies. The FDA recommends that healthcare professionals measure serum bicarbonate before starting treatment and periodically during treatment with zonisamide, even in the absence of symptoms. More information available: http://www.fda.gov/cder/drug/InfoSheets/HCP/zonisamideHCP.htm</p>
<p>Insulin Pens</p>	<p><u>Insulin Pens: Risk of Transmission of Blood-borne Pathogens from Shared Use [Posted 03/19/2009]</u></p> <p>The FDA notified healthcare providers and patients that sharing of insulin pens may result in transmission of hepatitis viruses, HIV, or other blood-borne pathogens. Insulin pens are not designed, and are not safe, for use in more than one patient, even if needles are changed between patients because any blood contamination of the pen reservoir could result in transmission of already existing blood-borne pathogens from the previous user. Insulin pens are designed to be safe for one patient to use one pen multiple times with a new, fresh needle for each injection. http://www.fda.gov/bbs/topics/NEWS/2009/NEW01976.html</p>
<p>Afinitor® (everolimus)</p>	<p><u>New Drug Approval for Advanced Kidney Cancer (posted 4/3/2009)</u></p> <p>Novartis International AG received FDA approval on Afinitor oral tablets (everolimus), a selective mTOR protein kinase inhibitor, for the treatment of patients with advanced kidney cancer. The drug is intended for those patients with advanced renal cell cancer whose disease has progressed after therapy with a non-selective kinase inhibitor. http://www.fda.gov/bbs/topics/NEWS/2009/NEW01980.html</p>
<p>Raptiva® (efalizumab)</p>	<p><u>FDA Statement on the Voluntary Withdrawal of Raptiva From the U.S. Market (posted 4/8/2009)</u></p> <p>Genentech and FDA notified healthcare professionals of the voluntary, phased withdrawal of Raptiva, a medication for treatment of psoriasis, from the U.S. market due to a potential risk to patients of developing progressive multifocal leukoencephalopathy (PML). By June 8, 2009, Raptiva will no longer be available in the United States. Prescribers are being asked not to initiate Raptiva treatment for any new patients. Prescribers should immediately begin discussing with patients currently using Raptiva how to transition to alternative therapies. http://www.fda.gov/bbs/topics/NEWS/2009/NEW01992.html</p>

ACCF/AHA: 2009 FOCUSED UPDATE GUIDELINE FOR THE DIAGNOSIS & MANAGEMENT OF HEART FAILURE IN ADULTS⁴

The American College of Cardiology Foundation (ACCF) and The American Heart Association (AHA) recently published a focused updated of the 2005 Guideline for the Management of Patients with Chronic Heart Failure incorporating new clinical trial evidence since the last update in 2005. This focused update was approved for publication by ACCF and AHA and endorsed by the International Society for Heart and Lung Transplantation. Envision Rx recognizes the importance of the new clinical guidelines updates and includes the following study highlights:

- Clarification of the functional assessment of the HF patient into ACA/AHA Stages of Heart Failure.
- A modified recommendation indicating that measurement of natriuretic peptides (BNP and NT-proBNP) can be useful in the evaluation of patients whom the clinical diagnosis of heart failure is uncertain and that measurement of natriuretic peptides (BNP and NT-proBNP) can be useful in risk stratification used with other clinical factors.
- Strengthened recommendations for the use of hydralazine and isosorbide dinitrate to improve outcomes in African American patients with New York Heart Association class III or IV symptoms who are receiving optimal therapy with angiotensin-converting enzyme inhibitors, beta-blockers, and diuretics.
- Clarification of treatment goals for patients with heart failure and atrial fibrillation; either maintain sinus rhythm or control ventricular rate. Trial data showed no preference in treatment strategies.
- Changes in the recommendations about electrical device therapy to make the guidelines consistent with the ACC/ANA/Heart Rhythm Society 2008 device based therapy guidelines.
- A recommendation against routine intermittent outpatient infusions of vasoactive and positive inotropic agents for patients with refractory end-stage heart failure.
- The addition of a new section on managing patients hospitalized with heart failure.

A T R I S K H F S T A T U S	Stage A	<ul style="list-style-type: none"> • Treat risk factors for heart failure • Identify and avoid heart toxins (ie. Illicit/improper drug use) • Drugs Therapy: Initiate ACE inhibitor or ARB in select patients based on risk factors (i.e. vascular disease, diabetes)
	Stage B (similar to NYHA Class I)	<ul style="list-style-type: none"> • All measures under Stage A • May consider implantable defibrillators in select patients • Drugs for routine use: ACE inhibitor or ARB and/or initiate beta blockers in select patients based on risk factors
	Stage C (similar to NYHA Class II and Class III)	<ul style="list-style-type: none"> • All measures under Stages A and B • May consider implantable defibrillators, biventricular spacing in select patients. • Drugs for routine use: ACE inhibitor or ARB, beta blockers, diuretics and/or digoxin. May consider aldosterone antagonist, hydralazine/ nitrates in select patients.
	Stage D (similar to NYHA Class IV)	<ul style="list-style-type: none"> • All measures under stages A, B, and C • Hospice/Palliative therapy • Experimental surgery and/or drugs, heart transplant

A comprehensive summary of the ACCF/AHA Heart Failure Treatment Guideline, is available at Circulation 2009

NEW GENERIC DRUG APPROVALS

Brand-name drug	Generic-name drug	Dosage Forms/Strengths	Therapeutic Drug Class	Approval Date	Manufacturer
DEPAKOTE ER	DIVALPROEX SODIUM	250 MG, 500 MG Extended Release Tablets	Anticonvulsant	1/29/2009	MYLAN PHARMACEUTICALS, INC.
NIRAVAM	ALPRAZOLAM	0.25 MG, 0.5 MG, 1 MG, 2 MG Orally Disintegrating Tablets	Benzodiazepine	1/9/2009	KALI LABORATORIES, INC.
SOLODYN	MINOCYCLINE HYDROCHLORIDE	45 MG, 90 MG, 135 MG Extended Release Tablets	Tetracycline Antibiotic	2/3/2009	IMPAX LABORATORIES, INC.
IMITREX	SUMATRIPTAN SUCCINATE	25 MG, 50 MG, 100 MG Tablets	Antimigraine	2/9/2009	TEVA PHARMACEUTICALS USA
YAZ	DROSPIRENONE AND ETHINY ESTRADIOL	3 MG/0.02 MG Tablets (28 DAY REGIME)	Oral Contraceptive	3/30/2009	BARR LABORATORIES INC.

Source: FDA, Office of Generic Drugs, First Time Generics available: <http://www.fda.gov/cder/ogd/approvals/default.htm>

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- [Preferred Drug List](#)
- [Health & Drug Information](#)
- [Adverse Reaction Reporting](#)
- [Professional Comment Form](#)
- [Customer Service Information](#)



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4. Abraham WT, et al. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*, Apr 2009; 119: 1977 - 2016.