CARDIOVASCULAR

PHARMACOGENETIC

GENOTYPING PANEL

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About the Test

Pharmacogenetics is the study of genetic determinants of interindividual drug response variability, and accumulating evidence supporting clinical utility for certain pharmacogenetic variants has prompted recent genotype-directed clinical practice recommendations for selected gene/drug pairs. Sema4 has designed and validated a Cardiovascular Pharmacogenetic (PGx) Genotyping Panel that is intended to help physicians prescribe selected medications that can be influenced by interindividual genetic variability. The panel includes 82 variants in 11 genes (including intergenic regions). These genes and variants in the clinical PGx panel inform on 23 medications used across this clinical specialty.

The Sema4 Cardiovascular PGx Genotyping Panel is intended for adults and older children. Please note that a Sema4 Pediatric Pharmacogenetic (PGx) Genotyping panel is also available for children.

Indications

The Sema4 Cardiovascular PGx Genotyping panel is intended to provide medication recommendations and drug response information to health care providers based on pharmacogenetic results. The information provided from this panel may help physicians make more informed management decisions regarding drug administration. **Please note that any modification of therapy should only be performed as directed by a healthcare professional.**

Testing Methods, Sensitivity, and Limitations

Targeted genotyping is performed for this test using multiplex Polymerase Chain Reaction (PCR) and multiplex Single Base Extension (SBE) reaction with Agena® SpectroCHIP® II on a MassARRAY® Analyzer 4 system. In addition, Multiplex ligation-dependent probe amplification (MLPA) serves as an adjunct test to interrogate copy number variants in the *CYP2C19, CYP2C9, CYP2D6,* and *CYP3A4* genes. Resources including the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines, FDA drug label recommendations, and peer-reviewed literature are used in the interpretation of these PGx testing results.

The analytical sensitivity and specificity of this assay is estimated to be greater than 99%. Only genes and variants included in this panel will be detected and reported. This test does not detect all the known alleles that result in altered or inactive gene function. This test does not account for all genetic variants in tested individuals. Absence of a detected gene variant with this panel does not rule out the possibility that a patient will have an atypical drug response phenotype, which could be due to an untested genetic variant or other factors such as drug-drug interactions, comorbidities, and/or other clinical and environmental variables.

Turnaround Time

Results are reported to the referring physician within 7-10 business days from the receipt of the specimen.

Specimen and Shipping Requirements

blood samples: Two lavender-top (EDTA) or two yellow-top (ACD-A or ACD-B) tubes, 5-10 mL of blood from the patient are required.
Tubes of blood should be kept and shipped refrigerated or at room temperature (PLEASE DO NOT FREEZE).

Extracted DNA samples: We request 50 µL DNA (50-250 ng/µL) or at minimum require 20 µL DNA (50-250 ng/µL). Causes for rejection include impurities in the test or reference DNA samples, including NaCl or KCl (>40 mM) and other salts, phenol, ethanol, heparin, EDTA (>1.5 mM), and Fe, contaminated DNA, and low concentration of DNA (<20 ng/µL).

Saliva samples: We can accept saliva specimens upon request. Saliva samples should be collected in Oragene DNA (OG-500) kits by DNA Genotek. Please contact our laboratory to obtain saliva kits.

Customer Services and Genetic Counseling

Include the following with each sample:
• Completed and signed test requisition form and informed consent
• Billing information or payment (include copy of insurance card)
• Contact information for referring physician
• Testing to be performed (Cardiovascular PGx Panel)
• Indication for testing, patient's family history, ethnic background and prior relevant test results

Send same day *or overnight (check for morning delivery)* to:
Sema4
62 Southfield Avenue
Stamford, CT 06902

Contact:
gc@sema4.com
Tel: 800-298-6470
Fax: 646-859-6871

Disclaimer

This test was developed and its performance characteristics were determined by Sema4 and was considered acceptable for patient testing. It has not been cleared or approved by the FDA. The FDA has determined that such clearance or approval is not necessary. This type of mutation analysis generally provides highly accurate genotype information for single nucleotide variants and small insertion/deletion variants. Despite this level of accuracy, it should be kept in mind that there are many potential sources of diagnostic error, including misidentification of samples, rare polymorphisms, or other rare genetic variants that interfere with analysis. In addition, families should understand the limitations of the testing and that rare diagnostic errors may occur for the reasons described.

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MEDICATION LIST

Atorvastatin

Atorvastatin (Lipitor®) is a member of the drug class known as statins. It is used for lowering cholesterol. Atorvastatin is a competitive inhibitor of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-determining enzyme in cholesterol biosynthesis via the mevalonate pathway. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate. Atorvastatin acts primarily in the liver. Decreased hepatic cholesterol levels increases hepatic uptake of cholesterol and reduces plasma cholesterol levels. Atorvastatin is metabolized through the CYP3A4 enzyme pathway. Preliminary studies have shown that polymorphisms in the gene that codes this enzyme can affect response to the medication. SLC01B1 is also a transporter of this medication and polymorphisms in this gene can cause plasma concentrations to be affected.
References:PMID: 19802823, 22120734, 23361102

Azilsartan

Azilsartan (Edarbi®) is an angiotensin receptor blocker (ARB) and indicated for the treatment of hypertension alone or as an adjunct. Azilsartan medoxomil blocks the angiotensin II type 1 receptor preventing angiotensin II from binding and causing vasoconstriction. Azilsartan's ability to remain tightly bound to AT1 receptors for very long periods after drug washout is among its most unusual features. Azilsartan is metabolized by CYP2C9. CYP2C9 carries out decarboxylation of azilsartan to M-I, and O-dealkylation of azilsartan to M-II. Both M-I and M-II have no pharmacologic activity.
References: DrugBank, DailyMed FDA-approved drug label

Carvedilol

Carvedilol (Coreg®) is a nonselective beta-adrenergic blocking agent with alpha1-blocking activity and is indicated for the treatment of hypertension and mild or moderate (NYHA class II or III) heart failure of ischemic or cardiomyopathic origin. Carvedilol's beta-adrenergic receptor blocking ability decreases the heart rate, myocardial contractility, and myocardial oxygen demand. Carvedilol also decreases systemic vascular resistance via its alpha adrenergic receptor blocking properties. Carvedilol is metabolized by CYP2D6 and CYP2C9. The drug label states that carvedilol is affected by the poor metabolizers of debrisoquine (a marker for cytochrome P450 2D6) resulting in higher plasma concentrations of R(+)-carvedilol. Additionally, retrospective analysis of side effects in clinical trials showed that CYP2D6 poor metabolizers had a higher rate of dizziness during up-titration, presumably resulting from vasodilating effects of the higher concentrations of the a-blocking R(+) enantiomer.
References: FDA reference ID 3828699

Clonidine

Clonidine (Catapres®) is an imidazoline-derivative hypotensive agent is a centrally-acting α2-adrenergic agonist. Clonidine may be used as an adjunct in the treatment of hypertension, as an epidural infusion as an adjunct treatment in the management of severe cancer pain that is not relieved by opiate analgesics alone, for differential diagnosis of pheochromocytoma in hypertensive patients, prophylaxis of vascular migraine headaches, treatment of severe

dysmenorrhea, management of vasomotor symptoms associated with menopause, rapid detoxification in the management of opiate withdrawal, treatment of alcohol withdrawal used in conjunction with benzodiazepines, management of nicotine dependence, topical use to reduce intraocular pressure in the treatment of open-angle and secondary glaucoma and hemorrhagic glaucoma associated with hypertension, and in the treatment of attention-deficit hyperactivity disorder (ADHD). Clonidine is an α-adrenergic agent that acts specifically on α2-receptors. α2-receptors regulate a number of signaling pathways mediated by multiple Gi proteins, Gαi1, Gαi2, and G&alphai3. The α2A- and α2C-receptors are located presynaptically and inhibit the released of noradrenaline from sympathetic nerves. Stimulation of these receptors decreases sympathetic tone, resulting in decreases in blood pressure and heart rate. It has been shown that the CYP2D6 enzyme has a role in the metabolism of clonidine. Individuals with a variant in the CYP2D6 gene either increasing or decreasing function can have a subtherapeutic response or increased risk for adverse reactions, respectively.
References: DailyMed FDA-approved drug label, DrugBank, PMID: 20570945

Clopidogrel

Clopidogrel (Plavix®) is an antiplatelet agent prescribed for prevention of ischemic events resulting from acute coronary syndromes (ACS), ischemic stroke, and symptomatic peripheral artery disease (PAD). Clopidogrel is biotransformed in the liver to an active metabolite that binds specifically and irreversibly to the platelet P2Y12 receptor, inhibiting ADP-mediated platelet activation and aggregation. Interindividual variability in platelet aggregation is common during clopidogrel therapy and individuals who carry variant CYP2C19 alleles have increased risks for reduced active clopidogrel metabolites, higher on-treatment platelet aggregation, and major adverse cardiovascular events. Current guidelines recommend alternative antiplatelet agents for ACS patients undergoing percutaneous coronary intervention (PCI) who carry decreased function CYP2C19 alleles.
References: PMID: 23698643, 21412232

Flecainide

Flecainide (Tambocor®) is an antiarrhythmic agent, class 1c, and is indicated for the treatment/prevention of ventricular arrhythmias, paroxysmal atrial fibrillation/flutter and paroxysmal supraventricular tachycardias and also atrial fibrillation or flutter (off-label). Flecainide slows conduction in cardiac tissue by altering transport of ions across cell membranes; causes slight prolongation of refractory periods; decreases the rate of rise of the action potential without affecting its duration; increases electrical stimulation threshold of ventricle, His-Purkinje system; possesses local anesthetic and moderate negative inotropic effects. Flecainide's major metabolic pathway is through the CYP2D6 enzyme system. Guidelines suggest that if an individual's phenotype is that of a CYP2D6 intermediate metabolizer the flecainide dose should be reduced by 25%. If the individual's phenotype is that of a CYP2D6 poor metabolizer the flecainide dose should be reduced by 50%.
References: PMID: 21412232

Fluvastatin

Fluvastatin (Lescol®) is an antilipemic agent that competitively inhibits hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonic acid, the rate-limiting step in cholesterol biosynthesis. Fluvastatin belongs to a class of medications called statins and is used to

reduce plasma cholesterol levels and prevent cardiovascular disease. It is also the first entirely synthetic HMG-CoA reductase inhibitor and is structurally distinct from the fungal derivatives of this therapeutic class. Fluvastatin is metabolized primarily by the CYP2C9 isozyme system (75%), and to a lesser extent by CYP3A4 (~20%) and CYP2C8 (~5%). Patients with the CC (CYP2C9*3/*3) genotype may have higher plasma levels of fluvastatin as compared to patients with the AC (CYP2C9*1/*3) or AA (CYP2C9*1/*1) genotype. The clinical effect of higher plasma concentrations is unknown.
References: FDA Labeling on Dailymed, PMID: 12891229

Irbesartan

Irbesartan (Avapro®) is an angiotensin receptor blocker (ARB) used mainly for the treatment of hypertension. Angiotensin II is a potent vasoconstrictor formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the primary vasoactive hormone of the renin-angiotensin system, and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Irbesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively binding to the AT1 angiotensin II receptor found in many tissues. Irbesartan is metabolized via glucuronide conjugation and oxidation. In vitro studies of irbesartan oxidation by cytochrome P450 isoenzymes indicated irbesartan was oxidized primarily by 2C9. Those individuals with CYP2C9 reduced function, or with poor metabolizer phenotype are expected to have reduced ability to metabolize the active compound and therefore have greater effect on their blood pressure.
References: DailyMed FDA-approved drug label, DrugBank**,** PMID: 21842338, 12359989

Losartan

Losartan (Cozaar®) is an angiotensin-receptor blocker (ARB) that may be used alone or with other agents to treat hypertension. Losartan competitively inhibits the binding of angiotensin II to AT1 in many tissues including vascular smooth muscle and the adrenal glands. Losartan is metabolized to its active metabolite, E-3174, which is 10 to 40 times more potent than losartan and acts as a non-competitive AT1 antagonist. Inhibition of angiotensin II binding to AT1 inhibits its AT1-mediated vasoconstrictive and aldosterone-secreting effects and results in decreased vascular resistance and blood pressure. Losartan is metabolized to a 5-carboxylic acid derivative (E-3174) via an aldehyde intermediate (E-3179) primarily by cytochrome P450 (CYP) 2C9 and CYP3A4. E-3174 is an active metabolite with 10- to 40-fold higher potency than its parent compound, losartan. Polymorphisms in CYP2C9 have been shown to have an effect on the pharmacokinetic parameters of the drug.
References: DrugBank, DailyMed FDA-approved
label, PMID: 25977991, 23171336, 23446815

Lovastatin

Lovastatin (Mevacor®) is a cholesterol-lowering agent that belongs to the class of medications called statins. It was the second agent of this class discovered. Lovastatin is a specific inhibitor of HMG-CoA reductase, the enzyme which catalyzes the conversion of HMG-CoA to mevalonate. The conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway for cholesterol. Lovastatin is hepatically metabolized in which the major active metabolites are the β-hydroxyacid of lovastatin, the 6'-hydroxy derivative, and two additional metabolites. The principle CYP enzyme involved is CYP3A4. It has also been shown that individuals with polymorphisms in their SLC01B1 gene can have elevated plasma

levels of lovastatin acid. Increased exposure may be associated with therapeutic response and also adverse events such as muscle toxicity.
References: DailyMed FDA-approved drug label, DrugBank, PMID: 26020121, 16103896

Metoprolol

Metoprolol (Lopressor®, Toprol®) is a cardioselective beta1-adrenergic blocking agent. Metoprolol is indicated for the treatment of angina, atrial fibrillation/flutter, heart failure, hypertension, acute myocardial infarction (secondary prevention "off-label"). Metoprolol competes with adrenergic neurotransmitters such as catecholamines for binding at beta(1)-adrenergic receptors in the heart. Beta(1)-receptor blockade results in a decrease in heart rate, cardiac output, and blood pressure. Metoprolol is primarily metabolized by the CYP2D6 enzyme. Approximately 8% of Caucasians and 2% of most other populations have absent CYP2D6 activity and are known as "*CYP2D6* poor metabolizers." The FDA-approved drug label for metoprolol states that *CYP2D6* poor metabolizers, and normal metabolizers who concomitantly take drugs that inhibit CYP2D6, will have increased (several-fold) metoprolol blood levels, decreasing metoprolol's cardioselectivity (1). The Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP) has published metoprolol dosing recommendations based on *CYP2D6* genotype. For individuals who have a *CYP2D6* gene variation that reduces the conversion of metoprolol to inactive metabolites, DPWG states that the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia. For CYP2D6 poor metabolizers, if a gradual reduction in heart rate is desired, or in the event of symptomatic bradycardia, DPWG recommends increasing the dose of metoprolol in smaller steps and/or prescribing no more than 25% of the standard dose. For other cases, no action is required.
References: FDA-approved drug label, PMID: 28520381, 21412232

Mexiletine

Mexiletine (Mexitil®) is an antiarrhythmic agent indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that, in the judgement of the physician, are life-threatening. Mexiletine is a Class 1B antiarrhythmic compound with electrophysiologic properties like those of lidocaine, but dissimilar from quinidine, procainamide, and disopyramide. Mexiletine has been shown to be effective in the suppression of induced ventricular arrhythmias, including those induced by glycoside toxicity and coronary artery ligation. Mexiletine, like lidocaine, inhibits the inward sodium current, thus reducing the rate of rise of the action potential, Phase 0. Mexiletine is mainly metabolized in the liver, the primary pathway being CYP2D6 metabolism, although it is also a substrate for CYP1A2. With involvement of CYP2D6, there can be either poor or extensive metabolizer phenotypes.
References: FDA drug labeling on Dailymed

Nebivolol

Nebivolol (Bystolic®) is a highly cardioselective vasodilatory beta1 receptor blocker used in treatment of hypertension. Activation of β1-receptors by epinephrine increases the heart rate and the blood pressure, and the heart consumes more oxygen. Nebivolol blocks these receptors which reverses the effects of epinephrine, lowering the heart rate and blood pressure. In addition, beta blockers prevent the release of renin, which is a hormone produced by the kidneys which leads to constriction of blood vessels. Nebivolol is metabolized by a

number of routes, including glucuronidation and hydroxylation by CYP2D6. The active isomer (d-nebivolol) has an effective half-life of about 12 hours in CYP2D6 extensive metabolizers (most people), and 19 hours in poor metabolizers and exposure to d-nebivolol is substantially increased in poor metabolizers. FDA labeling states that, though it is metabolized by CYP2D6, no dose adjustments are necessary for CYP2D6 poor metabolizers, as the clinical effect and safety profile was similar between poor and extensive metabolizers.
References: FDA Labeling from DailyMed, DrugBank

Pitavastatin

Pitavastatin (Livalo®) is an antilipemic agent prescribed to lower serum levels of total cholesterol, LDL-C, apolipoprotein B, and triglycerides, and raise levels of HDL-C for the treatment of dyslipidemia. Pitavastatin is a competitive inhibitor of the liver enzyme, HMG-CoA reductase. The SLCO1B1 gene encodes a protein responsible for the influx of pitavastatin. Variants in this gene are associated with higher pitavastatin plasma levels.
References:PMID: 20175818

Pravastatin

Pravastatin (Pravachol®) is an antilipemic agent prescribed to lower serum levels of total cholesterol, LDL-C, apolipoprotein B, and triglycerides, and raise levels of HDL-C for the treatment of dyslipidemia. Pravastatin is a competitive inhibitor of the liver enzyme, HMG-CoA reductase. The *SLCO1B1* gene encodes a protein responsible for the influx of pravastatin. Variants in this gene are associated with higher pravastatin plasma levels.
References: PMID: 19776292, 17622941

Propafenone

Propafenone (Rythmol®) is an antiarrhythmic agent prescribed for cardiac arrhythmia. Propafenone acts through a reduction of upstroke velocity (Phase 0) of the monophasic action potential. In Purkinje fibers, and to a lesser extent myocardial fiber, propafenone reduces the fast inward current carried by sodium ions. Diastolic excitability threshold is increased and effective refractory period prolonged. It is metabolized by CYP2D6, CYP3A4 and CYP1A2 isoenzymes. Variants in CYP2D6 gene can alter the enzymatic activity. Poor metabolizers are expected to have increased plasma levels of drug. Current guidelines recommend reducing the dose of propafenone by 70% for CYP2D6 poor metabolizers, and adjust propafenone dose according to plasma concentrations or use an alternative drug for CYP2D6 intermediate and ultrarapid metabolizers.
References: PMID: 21412232, FDA-approved drug label
https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/019151s012lbl.pdf

Propranolol

Propranolol (Inderal®) is a widely used non-cardioselective beta-adrenergic antagonist. Propranolol is indicated for the treatment or prevention of many disorders including acute myocardial infarction, arrhythmias, angina pectoris, hypertension, hypertensive emergencies, hyperthyroidism, migraine, pheochromocytoma, menopause, and anxiety. Propranolol competes with sympathomimetic neurotransmitters such as catecholamines for binding at beta(1)-adrenergic receptors in the heart, inhibiting sympathetic stimulation. This results in a reduction in resting heart rate, cardiac output, systolic and diastolic blood pressure, and reflex orthostatic hypotension. *In-vitro* studies have indicated that the aromatic hydroxylation of propranolol is catalyzed mainly by polymorphic

CYP2D6. Side-chain oxidation is mediated mainly by CYP1A2 and to some extent by CYP2D6. 4-hydroxy propranolol is a weak inhibitor of CYP2D6. In healthy subjects, no difference was observed between CYP2D6 extensive metabolizers (EMs) and poor metabolizers (PMs) with respect to oral clearance or elimination half-life. Partial clearance of 4-hydroxy propranolol was significantly higher and naphthyloxylactic acid was significantly lower in EMs than PMs.
References: FDA drug label on DailyMed, DrugBank, PMID: 9399616

Ranolazine

Ranolazine (Ranexa®) is an antianginal agent prescribed for the treatment of chronic angina. Ranolazine inhibits the late phase of the inward sodium channel in ischemic cardiac myocytes during cardiac repolarization reducing intracellular sodium concentrations and thereby reducing calcium influx via Na^{+}-Ca^{2+} exchange. The risk for increased exposure leading to adverse events is higher in patients lacking CYP2D6 activity (poor metabolizers, PM) than subjects with CYP2D6 metabolizing capacity (extensive metabolizers, EM). Current guidelines state that there is a lower need for precautions in patients who are CYP2D6 normal metabolizers.
References: EMA-approved drug label
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000805/WC500045937.pdf

Rosuvastatin

Rosuvastatin (Crestor®) is an antilipemic agent that competitively inhibits hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonic acid, the rate-limiting step in cholesterol biosynthesis. Rosuvastatin belongs to a class of medications called statins and is used to reduce plasma cholesterol levels and prevent cardiovascular disease. Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter organic anion-transporting polyprotein 1B1 (OATP1B1) which is encoded by the gene *SLC01B1*. Polymorphisms in this gene have been shown to increase plasma concentrations, which can increase the risk of myopathy.
References: DailyMed FDA-approved drug label, DrugBank, PMID: 17473846, 28385543

Simvastatin

Simvastatin (Zocor®) is an antilipemic agent prescribed for treatment of hypercholesterolemia and for the reduction in the risk of cardiac heart disease mortality and cardiovascular events. Simvastatin acts through inhibition of HMG-CoA reductase. In patients with variants in SLCO1B1 gene, there are modest increases in myopathy risk even at lower simvastatin doses (40 mg daily). Current guidelines recommend prescribing a lower dose or considering an alternative statin for patients who have variants in SLCO1B1 gene.
References: PMID: 22617227, 24918167

Timolol

Timolol (Timoptic®, Betimol®) is a beta-adrenergic antagonist similar in action to propranolol. The levo-isomer is the more active. Timolol has been proposed as an antihypertensive, antiarrhythmic, antiangina, and antiglaucoma agent. It is also used in the treatment of migraine disorders and tremor. Timolol competes with adrenergic neurotransmitters such as catecholamines for binding at beta(1)-adrenergic receptors in the heart and vascular smooth muscle and beta(2)-receptors in the bronchial and vascular

smooth muscle. Beta(1)-receptor blockade results in a decrease in resting and exercise heart rate and cardiac output, a decrease in both systolic and diastolic blood pressure, and, possibly, a reduction in reflex orthostatic hypotension. Beta(2)-blockade results in an increase in peripheral vascular resistance. The exact mechanism whereby timolol reduces ocular pressure is still not known. The most likely action is by decreasing the secretion of aqueous humor. Earlier clinical studies suggested that timolol is metabolized by CYP2D6, an important member of the cytochrome P450 family; however, CYP2C19 may also have a minor role. After topical administration, systemic timolol concentrations may be high enough to cause cardiovascular and respiratory adverse effects especially in patients who use concomitant CYP2D6 inhibitors or those who are CYP2D6 poor metabolizers.
References: FDA drug label on DailyMed, DrugBank, PMID: 21385322

Torsemide

Torsemide (Demadex®) is a diuretic agent prescribed for the treatment of edema associated with congestive heart failure, renal disease, or hepatic disease. Also, for the treatment of hypertension alone or in combination with other antihypertensive agents. Torsemide inhibits reabsorption of sodium and chloride in the ascending loop of Henle and distal renal tubule, interfering with the chloride-binding cotransport system, thus causing increased excretion of water, sodium, chloride, magnesium, and calcium. It is metabolized by CYP2C9 and polymorphisms in this gene may result in reduced clearance.
References: Drug Bank, UpToDate, FDA Label, PMID: 26344676, 16969365, 15592327

Warfarin

Warfarin (Coumadin®) is an anticoagulant used for the treatment of retinal vascular occlusion, pulmonary embolism, cardiomyopathy, atrial fibrillation and flutter, cerebral embolism, transient cerebral ischemia, arterial embolism and thrombosis. Warfarin acts by inhibiting the synthesis of vitamin K-dependent clotting factors, which include Factors II, VII, IX, and X, and the anticoagulant proteins C and S. A number of CYP450 isozymes are involved in the metabolism of warfarin. CYP2C9, a polymorphic enzyme, is likely to be the principal form of human liver CYP450 that modulates the *in vivo* anticoagulant activity of warfarin. Patients with one or more variant CYP2C9 alleles have decreased S-warfarin clearance. Also, VKORC1, the target enzyme for warfarin, is known to have several single nucleotide polymorphisms which are associated with warfarin dosing.
References: DailyMed FDA drug label, PMID 22010099