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USA

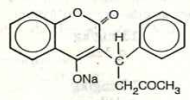
Shown in Product Identification Guide, page 310

ANTICOAGULANT

COUMADIN® TABLETS ℞
(Warfarin Sodium Tablets, USP) Crystalline
COUMADIN® FOR INJECTION
(Warfarin Sodium for Injection, USP)

DESCRIPTION

COUMADIN (crystalline warfarin sodium) is an anticoagulant which acts by inhibiting vitamin K-dependent coagulation factors. Chemically, it is 3-(α-acetonylbenzyl)-4-hydroxycoumarin and is a racemic mixture of the R- and S-enantiomers. Crystalline warfarin sodium is an isopropanol clathrate. The crystallization of warfarin sodium virtually eliminates trace impurities present in amorphous warfarin. Its empirical formula is $C_{19}H_{15}NaO_4$, and its structural formula may be represented by the following:



Crystalline warfarin sodium occurs as a white, odorless, crystalline powder, is discolored by light and is very soluble in water; freely soluble in alcohol; very slightly soluble in chloroform and in ether.

COUMADIN Tablets for oral use also contain:

All strengths:	Lactose, starch and magnesium stearate
1 mg:	D&C Red No. 6 Barium Lake
2 mg:	FD&C Blue No. 2 Aluminum Lake and FD&C Red No. 40 Aluminum Lake
2-1/2 mg:	D&C Yellow No. 10 Aluminum Lake and FD&C Blue No. 1 Aluminum Lake
3 mg:	FD&C Yellow No. 6 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake and FD&C Red No. 40 Aluminum Lake
4 mg:	FD&C Blue No. 1 Aluminum Lake
5 mg:	FD&C Yellow No. 6 Aluminum Lake
6 mg:	FD&C Yellow No. 6 Aluminum Lake and FD&C Blue No. 1 Aluminum Lake
7-1/2 mg:	D&C Yellow No. 10 Aluminum Lake and FD&C Yellow No. 6 Aluminum Lake
10 mg:	Dye Free

COUMADIN for Injection is supplied as a sterile, lyophilized powder, which, after reconstitution with 2.7 mL sterile Water for Injection, contains:

Warfarin Sodium	2 mg/mL
Sodium Phosphate, Dibasic, Heptahydrate	4.98 mg/mL
Sodium Phosphate, Monobasic, Monohydrate	0.194 mg/mL
Sodium Chloride	0.1 mg/mL
Mannitol	38.0 mg/mL
Sodium Hydroxide, as needed for pH adjustment to	8.1 to 8.3

CLINICAL PHARMACOLOGY

COUMADIN (Warfarin Sodium) and other coumarin anticoagulants act 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. Half-lives of these clotting factors are as follows: Factor II - 60 hours, VII - 4–6 hours, IX - 24 hours, and X - 48–72 hours. The half-lives of proteins C and S are approximately 8 hours and 30 hours, respectively. The resultant *in vivo* effect is a sequential depression of Factors VII, IX, X and II activities. Vitamin K is an essential cofactor for the post ribosomal synthesis of the vitamin K dependent clotting factors. The vitamin promotes the biosynthesis of γ-carboxyglutamic acid residues in the proteins which are essential for biological activity. Warfarin is thought to interfere with clotting factor synthesis by inhibition of the regeneration of vitamin K_1 epoxide. The degree of depression is dependent upon the dosage administered. Therapeutic doses of warfarin decrease the total amount of the active form of each vitamin K dependent clotting factor made by the liver by approximately 30% to 50%.

An anticoagulation effect generally occurs within 24 hours after drug administration. However, peak anticoagulant effect may be delayed 72 to 96 hours. The duration of action of a single dose of racemic warfarin is 2 to 5 days. The effects of COUMADIN (Warfarin Sodium) may become more pronounced as effects of daily maintenance doses overlap. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombus has occurred, the goal of anticoagulant treatment is to prevent further extension of the formed clot and prevent secondary thromboembolic complications which may result in serious and possibly fatal sequelae.

TABLE 1. CLINICAL STUDIES OF WARFARIN IN NON-RHEUMATIC AF PATIENTS*

Study	N				Thromboembolism		% Major Bleeding	
	Warfarin-Treated Patients	Control Patients	PT Ratio	INR	% Risk Reduction	*p*-value	Warfarin-Treated Patients	Control Patients
AFASAK	335	336	1.5–2.0	2.8–4.2	60	0.027	0.6	0.0
SPAF	210	211	1.3–1.8	2.0–4.5	67	0.01	1.9	1.9
BAATAF	212	208	1.2–1.5	1.5–2.7	86	<0.05	0.9	0.5
CAFA	187	191	1.3–1.6	2.0–3.0	45	0.25	2.7	0.5
SPINAF	260	265	1.2–1.5	1.4–2.8	79	0.001	2.3	1.5

* All study results of warfarin vs. control are based on intention-to-treat analysis and include ischemic stroke and systemic thromboembolism, excluding hemorrhage and transient ischemic attacks.

TABLE 2

Event	Warfarin (N=607)	Placebo (N=607)	RR (95% CI)	% Risk Reduction (p-value)
Total Patient Years of Follow-up	2018	1944		
Total Mortality	94 (4.7/100 py)	123 (6.3/100 py)	0.76 (0.60, 0.97)	24 (p=0.030)
Vascular Death	82 (4.1/100 py)	105 (5.4/100 py)	0.78 (0.60, 1.02)	22 (p=0.068)
Recurrent MI	82 (4.1/100 py)	124 (6.4/100 py)	0.66 (0.51, 0.85)	34 (p=0.001)
Cerebrovascular Event	20 (1.0/100 py)	44 (2.3/100 py)	0.46 (0.28, 0.75)	54 (p=0.002)

RR=Relative risk; Risk reduction=(I - RR); CI=Confidence interval; MI=Myocardial infarction; py=patient years

Pharmacokinetics: COUMADIN (Warfarin Sodium) is a racemic mixture of the R- and S-enantiomers. The S-enantiomer exhibits 2–5 times more anticoagulant activity than the R-enantiomer in humans, but generally has a more rapid clearance.

Absorption: COUMADIN (Warfarin Sodium) is essentially completely absorbed after oral administration with peak concentration generally attained within the first 4 hours.

Distribution: There are no differences in the apparent volumes of distribution after intravenous and oral administration of single doses of warfarin solution. Warfarin distributes into a relatively small apparent volume of distribution of about 0.14 liter/kg. A distribution phase lasting 6 to 12 hours is distinguishable after rapid intravenous or oral administration of an aqueous solution. Using a one compartment model, and assuming complete bioavailability, estimates of the volumes of distribution of R- and S-warfarin are similar to each other and to that of the racemate. Concentrations in fetal plasma approach the maternal values, but warfarin has not been found in human milk (see **WARNINGS—Lactation**). Approximately 99% of the drug is bound to plasma proteins.

Metabolism: The elimination of warfarin is almost entirely by metabolism. COUMADIN (Warfarin Sodium) is stereoselectively metabolized by hepatic microsomal enzymes (cytochrome P-450) to inactive hydroxylated metabolites (predominant route) and by reductases to reduced metabolites (warfarin alcohols). The warfarin alcohols have minimal anticoagulant activity. The metabolites are principally excreted into the urine; and to a lesser extent into the bile. The metabolites of warfarin that have been identified include dehydrowarfarin, two diastereoisomer alcohols, 4′-, 6-, 7-, 8- and 10-hydroxywarfarin. The cytochrome P-450 isozymes involved in the metabolism of warfarin include 2C9, 2C19, 2C8, 2C18, 1A2, and 3A4. 2C9 is likely to be the principal form of human liver P-450 which modulates the *in vivo* anticoagulant activity of warfarin.

Excretion: The terminal half-life of warfarin after a single dose is approximately one week; however, the effective half-life ranges from 20 to 60 hours, with a mean of about 40 hours. The clearance of R-warfarin is generally half that of S-warfarin, thus as the volumes of distribution are similar, the half-life of R-warfarin is longer than that of S-warfarin. The half-life of R-warfarin ranges from 37 to 89 hours, while that of S-warfarin ranges from 21 to 43 hours. Studies with radiolabeled drug have demonstrated that up to 92% of the orally administered dose is recovered in urine. Very little warfarin is excreted unchanged in urine. Urinary excretion is in the form of metabolites.

Elderly: Patients 60 years or older appear to exhibit greater than expected prothrombin time PT/INR response to the anticoagulant effects of warfarin. The cause of the increased sensitivity to the anticoagulant effects of warfarin in this age group is unknown. This increased anticoagulant effect from warfarin may be due to a combination of pharmacokinetic and pharmacodynamic factors. Racemic warfarin clearance may be unchanged or reduced with increasing age. Limited information suggests there is no difference in the clearance of S-warfarin in the elderly versus young subjects. However, there may be a slight decrease in the clearance of R-warfarin in the elderly as compared to the young. Therefore, as patient age increases, a lower dose of warfarin is usually required to produce a therapeutic level of anticoagulation.

Asians: Asian patients may require lower initiation and maintenance doses of warfarin. One non-controlled study conducted in 151 Chinese outpatients reported a mean daily warfarin requirement of 3.3 ± 1.4 mg to achieve an INR of 2 to 2.5. These patients were stabilized on warfarin for various indications. Patient age was the most important determinant of warfarin requirement in Chinese patients with a progressively lower warfarin requirement with increasing age.

Renal Dysfunction: Renal clearance is considered to be a minor determinant of anticoagulant response to warfarin. No dosage adjustment is necessary for patients with renal failure.

Hepatic Dysfunction: Hepatic dysfunction can potentiate the response to warfarin through impaired synthesis of clotting factors and decreased metabolism of warfarin.

The administration of COUMADIN (Warfarin Sodium) via the intravenous (IV) route should provide the patient with the same concentration of an equal oral dose, but maximum plasma concentration will be reached earlier. However, the full anticoagulant effect of a dose of warfarin may not be achieved until 72–96 hours after dosing, indicating that the administration of IV COUMADIN (Warfarin Sodium) should not provide any increased biological effect or earlier onset of action.

Clinical Trials

Atrial Fibrillation (AF): In five prospective randomized controlled clinical trials involving 3711 patients with non-rheumatic AF, warfarin significantly reduced the risk of systemic thromboembolism including stroke (See Table 1). The risk reduction ranged from 60% to 86% in all except one trial (CAFA: 45%) which stopped early due to published positive results from two of these trials. The incidence of major bleeding in these trials ranged from 0.6 to 2.7% (See Table 1). Meta-analysis findings of these studies revealed that the effects of warfarin in reducing thromboembolic events including stroke were similar at either moderately high INR (2.0–4.5) or low INR (1.4–3.0). There was a significant reduction in minor bleeds at the low INR. Similar data from clinical studies in valvular atrial fibrillation patients are not available.

[See table 1 above]

Myocardial Infarction: WARIS (The Warfarin Re-Infarction Study) was a double-blind, randomized study of 1214 patients 2 to 4 weeks post-infarction treated with warfarin to a target INR of 2.8 to 4.8. [But note that a lower INR was achieved and increased bleeding was associated with INR's above 4.0; (see **DOSAGE AND ADMINISTRATION**)]. The primary endpoint was a combination of total mortality and recurrent infarction. A secondary endpoint of cerebrovascular events was assessed. Mean follow-up of the patients was 37 months. The results for each endpoint separately, including an analysis of vascular death, are provided in the following table:

[See table 2 above]

Mechanical and Bioprosthetic Heart Valves: In a prospective, randomized, open label, positive-controlled study (Mok et al, 1985) in 254 patients, the thromboembolic-free interval was found to be significantly greater in patients with mechanical prosthetic heart valves treated with warfarin alone compared with dipyridamole-aspirin ($p<0.005$) and pentoxifylline-aspirin ($p<0.05$) treated patients. Rates of thromboembolic events in these groups were 2.2, 8.6, and 7.9/100 patient years, respectively. Major bleeding rates were 2.5, 0.0, and 0.9/100 patient years, respectively.

In a prospective, open label, clinical trial (Saour et al, 1990) comparing moderate (INR 2.65) vs. high intensity (INR 9.0) warfarin therapies in 258 patients with mechanical prosthetic heart valves, thromboembolism occurred with similar frequency in the two groups (4.0 and 3.7 events/100 patient years, respectively). Major bleeding was more common in the high intensity group (2.1 events/100 patient years) vs. 0.95 events/100 patient years in the moderate intensity group.

In a randomized trial (Turpie et al, 1988) in 210 patients comparing two intensities of warfarin therapy (INR

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2.0–2.25 vs. INR 2.5–4.0) for a three-month period following tissue heart valve replacement, thromboembolism occurred with similar frequency in the two groups (major embolic events 2.0% vs. 1.9%, respectively and minor embolic events 10.8% vs. 10.2%, respectively). Major bleeding complications were more frequent with the higher intensity (major hemorrhages 4.6%) vs. none in the lower intensity.

INDICATIONS AND USAGE

COUMADIN is indicated for the prophylaxis and/or treatment of venous thrombosis and its extension, and pulmonary embolism.

COUMADIN (Warfarin Sodium) is indicated for the prophylaxis and/or treatment of the thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement.

COUMADIN (Warfarin Sodium) is indicated to reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction.

CONTRAINDICATIONS

Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than the potential clinical benefits of anticoagulation, such as:

Pregnancy: COUMADIN (Warfarin Sodium) is contraindicated in women who are or may become pregnant because the drug passes through the placental barrier and may cause fatal hemorrhage to the fetus *in utero*. Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with warfarin during pregnancy.

Embryopathy characterized by nasal hypoplasia with or without stippled epiphyses (chondrodysplasia punctata) has been reported in pregnant women exposed to warfarin during the first trimester. Central nervous system abnormalities also have been reported, including dorsal midline dysplasia characterized by agenesis of the corpus callosum, Dandy-Walker malformation, and midline cerebellar atrophy. Ventral midline dysplasia, characterized by optic atrophy, and eye abnormalities have been observed. Mental retardation, blindness, and other central nervous system abnormalities have been reported in association with second and third trimester exposure. Although rare, teratogenic reports following *in utero* exposure to warfarin include urinary tract anomalies such as single kidney, asplenia, anencephaly, spina bifida, cranial nerve palsy, hydrocephalus, cardiac defects and congenital heart disease, polydactyly, deformities of toes, diaphragmatic hernia, corneal leukoma, cleft palate, cleft lip, schizencephaly, and microcephaly.

Spontaneous abortion and stillbirth are known to occur and a higher risk of fetal mortality is associated with the use of warfarin. Low birth weight and growth retardation have also been reported.

Women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks.

Hemorrhagic tendencies or blood dyscrasias.

Recent or contemplated surgery of: (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces.

Bleeding tendencies associated with active ulceration or overt bleeding of: (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms-cerebral, dissecting aorta; (4) pericarditis and pericardial effusions; (5) bacterial endocarditis.

Threatened abortion, eclampsia and preeclampsia.

Inadequate laboratory facilities.

Unsupervised patients with senility, alcoholism, or psychosis or other lack of patient cooperation.

Spinal puncture and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding.

Miscellaneous: major regional, lumbar block anesthesia, malignant hypertension and known hypersensitivity to warfarin or to any other components of this product.

WARNINGS

The most serious risks associated with anticoagulant therapy with warfarin sodium are hemorrhage in any tissue or organ and, less frequently (<0.1%), necrosis and/or gangrene of skin and other tissues. The risk of hemorrhage is related to the level of intensity and the duration of anticoagulant therapy. Hemorrhage and necrosis have in some cases been reported to result in death or permanent disability. Necrosis appears to be associated with local thrombosis and usually appears within a few days of the start of anticoagulant therapy. In severe cases of necrosis, treatment through debridement or amputation of the affected tissue, limb, breast or penis has been reported. Careful diagnosis is required to determine whether necrosis is caused by an underlying disease. Warfarin therapy should be discontinued when warfarin is suspected to be the cause of developing necrosis and heparin therapy may be considered for anticoagulation. Although various treatments have been attempted, no treatment for necrosis has been considered uniformly effective. See below for information on predisposing conditions. These and other risks associated with anticoagulant therapy must be weighed against the risk of thrombosis or embolization in untreated cases.

ENDOGENOUS FACTORS:

blood dyscrasias— see CONTRAINDICATIONS	diarrhea	hyperthyroidism
cancer	elevated temperature	poor nutritional state
collagen vascular disease	hepatic disorders	steatorrhea
congestive heart failure	infectious hepatitis	vitamin K deficiency
	jaundice	

EXOGENOUS FACTORS:

Potential drug interactions with COUMADIN are listed below by drug class and by specific drugs.

Classes of Drugs

5-lipoxygenase Inhibitor	Antineoplastics†	Fibric Acid Derivatives
Adrenergic Stimulants, Central	Antiparasitic/Antimicrobials	HMG-CoA Reductase Inhibitors†
Alcohol Abuse Reduction Preparations	Antiplatelet Drugs/Effects	Leukotriene Receptor Antagonist
Analgesics	Antithyroid Drugs†	Monoamine Oxidase Inhibitors
Anesthetics, Inhalation	Beta-Adrenergic Blockers	Narcotics, prolonged
Antiandrogen	Cholelitholytic Agents	Nonsteroidal Anti-Inflammatory Agents
Antiarrhythmics†	Diabetes Agents, Oral	Psychostimulants
Antibiotics†	Diuretics†	Pyrazolones
Aminoglycosides (oral)	Fungal Medications, Intravaginal, Systemic†	Salicylates
Cephalosporins, parenteral	Gastric Acidity and Peptic Ulcer Agents†	Selective Serotonin Reuptake Inhibitors
Macrolides	Gastrointestinal Prokinetic Agents	Steroids, Adrenocortical†
Miscellaneous	Ulcerative Colitis Agents	Steroids, Anabolic (17-Alkyl Testosterone Derivatives)
Penicillins, intravenous, high dose	Gout Treatment Agents	Thrombolytics
Quinolones (fluoroquinolones)	Hemorrheologic Agents	Thyroid Drugs
Sulfonamides, long acting	Hepatotoxic Drugs	Tuberculosis Agents†
Tetracyclines	Hyperglycemic Agents	Uricosuric Agents
Anticoagulants	Hypertensive Emergency Agents	Vaccines
Anticonvulsants†	Hypnotics†	Vitamins†
Antidepressants†	Hypolipidemics†	
Antimalarial Agents	Bile Acid-Binding Resins†	

Specific Drugs Reported

acetaminophen	fluconazole	penicillin G, intravenous
alcohol†	fluorouracil	pentoxifylline
allopurinol	fluoxetine	phenylbutazone
aminosalicylic acid	flutamide	phenytoin†
amiodarone HCl	fluvastatin	piperacillin
aspirin	fluvoxamine	piroxicam
atorvastatin†	gemfibrozil	pravastatin†
azithromycin	glucagon	prednisone†
capecitabine	halothane	propafenone
cefamandole	heparin	propoxyphene
cefazolin	ibuprofen	propranolol
cefoperazone	ifosfamide	propylthiouracil†
cefotetan	indomethacin	quinidine
cefoxitin	influenza virus vaccine	quinine
ceftriaxone	itraconazole	ranitidine†
celecoxib	ketoprofen	rofecoxib
cerivastatin	ketorolac	sertraline
chenodiol	levamisole	simvastatin
chloramphenicol	levofloxacin	stanozolol
chloral hydrate†	levothyroxine	streptokinase
chlorpropamide	liothyronine	sulfamethizole
cholestyramine†	lovastatin	sulfamethoxazole
cimetidine	mefenamic acid	sulfinpyrazone
ciprofloxacin	methimazole†	sulfisoxazole
cisapride	methyldopa	sulindac
clarithromycin	methylphenidate	tamoxifen
clofibrate	methylsalicylate ointment (topical)	tetracycline
COUMADIN overdose	metronidazole	thyroid
cyclophosphamide†	miconazole (intravaginal, systemic)	ticarcillin
danazol	moricizine hydrochloride†	ticlopidine
dextran	nalidixic acid	tissue plasminogen activator (t-PA)
dextrothyroxine	naproxen	tolbutamide
diazoxide	neomycin	tramadol
diclofenac	norfloxacin	trimethoprim/sulfamethoxazole
dicumarol	ofloxacin	urokinase
diflunisal	olsalazine	valproate
disulfiram	omeprazole	vitamin E
doxycycline	oxaprozin	zafirlukast
erythromycin	oxymetholone	zileuton
ethacrynic acid	paroxetine	
fenofibrate		
fenoprofen		

also: other medications affecting blood elements which may modify hemostasis
dietary deficiencies
prolonged hot weather
unreliable PT/INR determinations

†Increased and decreased PT/INR responses have been reported.

It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. COUMADIN (Warfarin Sodium), a narrow therapeutic range (index) drug, may be affected by factors such as other drugs and dietary vitamin K. Dosage should be controlled by periodic determinations of prothrombin time (PT)/International Normalized Ratio (INR) or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage PT. When heparin and COUMADIN are administered concomitantly, refer below to CONVERSION FROM HEPARIN THERAPY for recommendations.

Caution should be observed when COUMADIN is administered in any situation or in the presence of any predisposing condition where added risk of hemorrhage, necrosis, and/or gangrene is present.

Anticoagulation therapy with COUMADIN may enhance the release of atheromatous plaque emboli, thereby increasing the risk of complications from systemic cholesterol microembolization, including the "purple toes syndrome." Discontinuation of COUMADIN therapy is recommended when such phenomena are observed.

Systemic atheroemboli and cholesterol microemboli can present with a variety of signs and symptoms including purple toes syndrome, livedo reticularis, rash, gangrene, abrupt and intense pain in the leg, foot, or toes, foot ulcers, myalgia, penile gangrene, abdominal pain, flank or back pain, hematuria, renal insufficiency, hypertension, cerebral ischemia, spinal cord infarction, pancreatitis, symptoms simulating polyarteritis, or any other sequelae of vascular compro-

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Coumadin—Cont.

mise due to embolic occlusion. The most commonly involved visceral organs are the kidneys followed by the pancreas, spleen, and liver. Some cases have progressed to necrosis or death.

Purple toes syndrome is a complication of oral anticoagulation characterized by a dark, purplish or mottled color of the toes, usually occurring between 3–10 weeks, or later, after the initiation of therapy with warfarin or related compounds. Major features of this syndrome include purple color of plantar surfaces and sides of the toes that blanches on moderate pressure and fades with elevation of the legs; pain and tenderness of the toes; waxing and waning of the color over time. While the purple toes syndrome is reported to be reversible, some cases progress to gangrene or necrosis which may require debridement of the affected area, or may lead to amputation.

Heparin-induced thrombocytopenia: COUMADIN should be used with caution in patients with heparin-induced thrombocytopenia and deep venous thrombosis. Cases of venous limb ischemia, necrosis, and gangrene have occurred in patients with heparin-induced thrombocytopenia and deep venous thrombosis when heparin treatment was discontinued and warfarin therapy was started or continued. In some patients sequelae have included amputation of the involved area and/or death (Warkentin et al, 1997).

A severe elevation (>50 seconds) in activated partial thromboplastin time (aPTT) with a PT/INR in the desired range has been identified as an indication of increased risk of postoperative hemorrhage.

The decision to administer anticoagulants in the following conditions must be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the benefits:

Lactation: Based on very limited published data, warfarin has not been detected in the breast milk of mothers treated with warfarin. The same limited published data reports that some breast-fed infants, whose mothers were treated with warfarin, had prolonged prothrombin times, although not as prolonged as those of the mothers. The decision to breast-feed should be undertaken only after careful consideration of the available alternatives. Women who are breast-feeding and anticoagulated with warfarin should be very carefully monitored so that recommended PT/INR values are not exceeded. It is prudent to perform coagulation tests and to evaluate vitamin K status in infants at risk for bleeding tendencies before advising women taking warfarin to breast-feed. Effects in premature infants have not been evaluated.

Severe to moderate hepatic or renal insufficiency.

Infectious diseases or disturbances of intestinal flora: sprue, antibiotic therapy.

Trauma which may result in internal bleeding.

Surgery or trauma resulting in large exposed raw surfaces.

Indwelling catheters.

Severe to moderate hypertension.

Known or suspected deficiency in protein C mediated anticoagulant response: Hereditary or acquired deficiencies of protein C or its cofactor, protein S, have been associated with tissue necrosis following warfarin administration. Not all patients with these conditions develop necrosis, and tissue necrosis occurs in patients without these deficiencies. Inherited resistance to activated protein C has been described in many patients with venous thromboembolic disorders but has not yet been evaluated as a risk factor for tissue necrosis. The risk associated with these conditions, both for recurrent thrombosis and for adverse reactions, is difficult to evaluate since it does not appear to be the same for everyone. Decisions about testing and therapy must be made on an individual basis. It has been reported that concomitant anticoagulation therapy with heparin for 5 to 7 days during initiation of therapy with COUMADIN (Warfarin Sodium) may minimize the incidence of tissue necrosis. Warfarin therapy should be discontinued when warfarin is suspected to be the cause of developing necrosis and heparin therapy may be considered for anticoagulation.

Miscellaneous: polycythemia vera, vasculitis, and severe diabetes.

Minor and severe allergic/hypersensitivity reactions and anaphylactic reactions have been reported.

In patients with acquired or inherited warfarin resistance, decreased therapeutic responses to COUMADIN (Warfarin Sodium) have been reported. Exaggerated therapeutic responses have been reported in other patients.

Patients with congestive heart failure may exhibit greater than expected PT/INR response to COUMADIN (Warfarin Sodium), thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN (Warfarin Sodium).

Concomitant use of anticoagulants with streptokinase or urokinase is not recommended and may be hazardous. (Please note recommendations accompanying these preparations.)

PRECAUTIONS

Periodic determination of PT/INR or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medications, including botanicals, may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional

Classes of Drugs

Adrenal Corticol Steroid Inhibitors	Antithyroid Drugs†	HMG-CoA Reductase Inhibitors†
Antacids	Barbiturates	Immunosuppressives
Antianxiety Agents	Diuretics†	Oral Contraceptives, Estrogen Containing
Antiarrhythmics†	Enteral Nutritional Supplements	Selective Estrogen Receptor Modulators
Antibiotics†	Fungal Medications, Systemic†	Steroids, Adrenocortical†
Anticonvulsants†	Gastric Acidity and Peptic Ulcer Agents†	Tuberculosis Agents†
Antidepressants†	Hypnotics†	Vitamins†
Antihistamines	Hypolipidemics† Bile Acid-Binding Resins†	
Antineoplastics†		
Antipsychotic Medications		

Specific Drugs Reported

alcohol†	COUMADIN underdosage	phenytoin†
aminoglutethimide	cyclophosphamide†	pravastatin†
amobarbital	dicloxacillin	prednisone†
atorvastatin†	ethchlorvynol	primidone
azathioprine	glutethimide	propylthiouracil†
butabarbital	griseofulvin	raloxifene
butalbital	haloperidol	ranitidine†
carbamazepine	meprobamate	rifampin
chloral hydrate†	6-mercaptopurine	secobarbital
chlordiazepoxide	methimazole†	spironolactone
chlorthalidone	moricizine hydrochloride†	sucralfate
cholestyramine†	nafcillin	trazodone
clozapine	paraldehyde	vitamin C (high dose)
corticotropin	pentobarbital	vitamin K
cortisone	phenobarbital	

also: diet high in vitamin K
unreliable PT/INR determinations

†Increased and decreased PT/INR responses have been reported.

Botanicals that contain coumarins with potential anticoagulant effects:

Alfalfa	Celery	Parsley
Angelica (Dong Quai)	Chamomile (German and Roman)	Passion Flower
Aniseed	Dandelion[3]	Prickly Ash (Northern)
Arnica	Fenugreek	Quassia
Asa Foetida	Horse Chestnut	Red Clover
Bogbean[1]	Horseradish	Sweet Clover
Boldo	Licorice[3]	Sweet Woodruff
Buchu	Meadowsweet[1]	Tonka Beans
Capsicum[2]	Nettle	Wild Carrot
Cassia[3]		Wild Lettuce

Miscellaneous botanicals with anticoagulant properties:

Bladder Wrack (*Fucus*)	Pau d'arco	

Botanicals that contain salicylate and/or have antiplatelet properties:

Agrimony[4]	Dandelion[3]	Meadowsweet[1]
Aloe Gel	Feverfew	Onion[5]
Aspen	Garlic[5]	Policosanol
Black Cohosh	German Sarsaparilla	Poplar
Black Haw	Ginger	Senega
Bogbean[1]	Ginkgo Biloba	Tamarind
Cassia[3]	Ginseng (*Panax*)[5]	Willow
Clove	Licorice[3]	Wintergreen

Botanicals with fibrinolytic properties:

Bromelains	Garlic[5]	Inositol Nicotinate
Capsicum[2]	Ginseng (*Panax*)[5]	Onion[5]

Botanicals with coagulant properties:

Agrimony[4]	Mistletoe	
Goldenseal	Yarrow	

[1]Contains coumarins and salicylate.
[2]Contains coumarins and has fibrinolytic properties.
[3]Contains coumarins and has antiplatelet properties.
[4]Contains salicylate and has coagulant properties.
[5]Has antiplatelet and fibrinolytic properties.

PT/INR determinations in the period immediately after discharge from the hospital, and whenever other medications, including botanicals, are initiated, discontinued or taken irregularly. The following factors are listed for reference; however, other factors may also affect the anticoagulant response.

Drugs may interact with COUMADIN (Warfarin Sodium) through pharmacodynamic or pharmacokinetic mechanisms. Pharmacodynamic mechanisms for drug interactions with COUMADIN (Warfarin Sodium) are synergism (impaired hemostasis, reduced clotting factor synthesis), competitive antagonism (vitamin K), and altered physiologic control loop for vitamin K metabolism (hereditary resistance). Pharmacokinetic mechanisms for drug interactions with COUMADIN (Warfarin Sodium) are mainly enzyme induction, enzyme inhibition, and reduced plasma protein binding. It is important to note that some drugs may interact by more than one mechanism.

The following factors, alone or in combination, may be responsible for INCREASED PT/INR response:

[See table at top of previous page]

The following factors, alone or in combination, may be responsible for DECREASED PT/INR response:

ENDOGENOUS FACTORS:

edema	hypothyroidism
hereditary coumarin resistance	nephrotic syndrome
hyperlipemia	

EXOGENOUS FACTORS:

Potential drug interactions with COUMADIN (Warfarin Sodium) are listed below by drug class and by specific drugs.

[See first table above]

Because a patient may be exposed to a combination of the above factors, the net effect of COUMADIN (Warfarin Sodium) on PT/INR response may be unpredictable. More frequent PT/INR monitoring is therefore advisable. Medications of unknown interaction with coumarins are best regarded with caution. When these medications are started or stopped, more frequent PT/INR monitoring is advisable.

It has been reported that concomitant administration of warfarin and ticlopidine may be associated with cholestatic hepatitis.

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Botanical (Herbal) Medicines: Caution should be exercised when botanical medicines (botanicals) are taken concomitantly with COUMADIN (Warfarin Sodium). Few adequate, well-controlled studies exist evaluating the potential for metabolic and/or pharmacologic interactions between botanicals and COUMADIN (Warfarin Sodium). Due to a lack of manufacturing standardization with botanical medicinal preparations, the amount of active ingredients may vary. This could further confound the ability to assess potential interactions and effects on anticoagulation. It is good practice to monitor the patient's response with additional PT/INR determinations when initiating or discontinuing botanicals.

Specific botanicals reported to affect COUMADIN (Warfarin Sodium) therapy include the following:

- Bromelains, danshen, dong quai (*Angelica sinensis*), garlic, Ginkgo biloba, and ginseng are associated most often with an INCREASE in the effects of COUMADIN (Warfarin Sodium).
- Coenzyme Q_{10} (ubidecarenone) and St. John's wort are associated most often with a DECREASE in the effects of COUMADIN (Warfarin Sodium).

Some botanicals may cause bleeding events when taken alone (e.g., garlic and Ginkgo biloba) and may have anticoagulant, antiplatelet, and/or fibrinolytic properties. These effects would be expected to be additive to the anticoagulant effects of COUMADIN (Warfarin Sodium). Conversely, other botanicals may have coagulant properties when taken alone or may decrease the effects of COUMADIN (Warfarin Sodium).

Some botanicals that may affect coagulation are listed below for reference; however, this list should not be considered all-inclusive. Many botanicals have several common names and scientific names. The most widely recognized common botanical names are listed.

[See second table at top of previous page]

Effect on Other Drugs: Coumarins may also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (phenytoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

Special Risk Patients: COUMADIN (Warfarin Sodium) is a narrow therapeutic range (index) drug, and caution should be observed when warfarin sodium is administered to certain patients such as the elderly or debilitated or when administered in any situation or physical condition where added risk of hemorrhage is present.

Intramuscular (I.M.) injections of concomitant medications should be confined to the upper extremities which permits easy access for manual compression, inspections for bleeding and use of pressure bandages.

Caution should be observed when COUMADIN (Warfarin Sodium) (or warfarin) is administered concomitantly with nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, to be certain that no change in anticoagulation dosage is required. In addition to specific drug interactions that might affect PT/INR, NSAIDs, including aspirin, can inhibit platelet aggregation, and can cause gastrointestinal bleeding, peptic ulceration and/or perforation.

Acquired or inherited warfarin resistance should be suspected if large daily doses of COUMADIN (Warfarin Sodium) are required to maintain a patient's PT/INR within a normal therapeutic range.

Information for Patients: The objective of anticoagulant therapy is to decrease the clotting ability of the blood so that thrombosis is prevented, while avoiding spontaneous bleeding. Effective therapeutic levels with minimal complications are in part dependent upon cooperative and well-instructed patients who communicate effectively with their physician. Patients should be advised: Strict adherence to prescribed dosage schedule is necessary. Do not take or discontinue any other medication, including salicylates (e.g., aspirin and topical analgesics), other over-the-counter medications, and botanical (herbal) products (e.g., bromelains, coenzyme Q_{10}, danshen, dong quai, garlic, Ginkgo biloba, ginseng, and St. John's wort) except on advice of the physician. Avoid alcohol consumption. Do not take COUMADIN (Warfarin Sodium) during pregnancy and do not become pregnant while taking it (see **CONTRAINDICATIONS**). Avoid any activity or sport that may result in traumatic injury. Prothrombin time tests and regular visits to physician or clinic are needed to monitor therapy. Carry identification stating that COUMADIN (Warfarin Sodium) is being taken. If the prescribed dose of COUMADIN (Warfarin Sodium) is forgotten, notify the physician immediately. Take the dose as soon as possible on the same day but do not take a double dose of COUMADIN (Warfarin Sodium) the next day to make up for missed doses. The amount of vitamin K in food may affect therapy with COUMADIN (Warfarin Sodium). Eat a normal, balanced diet maintaining a consistent amount of vitamin K. Avoid drastic changes in dietary habits, such as eating large amounts of green leafy vegetables. Contact physician to report any illness, such as diarrhea, infection or fever. Notify physician immediately if any unusual bleeding or symptoms occur. Signs and symptoms of bleeding include: pain, swelling or discomfort, prolonged bleeding from cuts, increased menstrual flow or vaginal bleeding, nosebleeds, bleeding of gums from brushing, unusual bleeding or bruising, red or dark brown urine, red or tar black stools, headache, dizziness, or weakness. If therapy with COUMADIN (Warfarin Sodium) is discontinued, patients should be cautioned that the anticoagulant effects of COUMADIN (Warfarin Sodium) may persist for about 2 to 5 days. **Patients should be informed that all warfarin sodium, USP, products represent the same medication, and should not be taken concomitantly, as overdosage may result.**

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity and mutagenicity studies have not been performed with COUMADIN (Warfarin Sodium). The reproductive effects of COUMADIN (Warfarin Sodium) have not been evaluated.

Use in Pregnancy: Pregnancy Category X—See **CONTRAINDICATIONS**.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 18 have not been established, in randomized, controlled clinical trials. However, the use of COUMADIN (Warfarin Sodium) in pediatric patients is well-documented for the prevention and treatment of thromboembolic events. Difficulty achieving and maintaining therapeutic PT/INR ranges in the pediatric patient has been reported. More frequent PT/INR determinations are recommended because of possible changing warfarin requirements.

Geriatric Use: Patients 60 years or older appear to exhibit greater than expected PT/INR response to the anticoagulant effects of warfarin (see **CLINICAL PHARMACOLOGY**). COUMADIN (Warfarin Sodium) is contraindicated in any unsupervised patient with senility. Caution should be observed with administration of warfarin sodium to elderly patients in any situation or physical condition where added risk of hemorrhage is present. Lower initiation and maintenance doses of COUMADIN (Warfarin Sodium) are recommended for elderly patients (see **DOSAGE AND ADMINISTRATION**).

TABLE 3
Relationship Between INR and PT Ratios
For Thromboplastins With Different ISI Values (Sensitivities)

	PT RATIOS				
	ISI 1.0	ISI 1.4	ISI 1.8	ISI 2.3	ISI 2.8
INR = 2.0–3.0	2.0–3.0	1.6–2.2	1.5–1.8	1.4–1.6	1.3–1.5
INR = 2.5–3.5	2.5–3.5	1.9–2.4	1.7–2.0	1.5–1.7	1.4–1.6

ADVERSE REACTIONS

Potential adverse reactions to COUMADIN (Warfarin Sodium) may include:

- Fatal or nonfatal hemorrhage from any tissue or organ. This is a consequence of the anticoagulant effect. The signs, symptoms, and severity will vary according to the location and degree or extent of the bleeding. Hemorrhagic complications may present as paralysis; paresthesia; headache, chest, abdomen, joint, muscle or other pain; dizziness; shortness of breath, difficult breathing or swallowing; unexplained swelling; weakness; hypotension; or unexplained shock. Therefore, the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with PT/INR. (See **OVERDOSAGE—Treatment**.)
- Bleeding which occurs when the PT/INR is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g., tumor, ulcer, etc.
- Necrosis of skin and other tissues. (See **WARNINGS**.)
- Adverse reactions reported infrequently include: hypersensitivity/allergic reactions, systemic cholesterol microembolization, purple toes syndrome, hepatitis, cholestatic hepatic injury, jaundice, elevated liver enzymes, vasculitis, edema, fever, rash, dermatitis, including bullous eruptions, urticaria, abdominal pain including cramping, flatulence/bloating, fatigue, lethargy, malaise, asthenia, nausea, vomiting, diarrhea, pain, headache, dizziness, taste perversion, pruritus, alopecia, cold intolerance, and paresthesia including feeling cold and chills.

Rare events of tracheal or tracheobronchial calcification have been reported in association with long-term warfarin therapy. The clinical significance of this event is unknown. Priapism has been associated with anticoagulant administration, however, a causal relationship has not been established.

OVERDOSAGE

Signs and Symptoms: Suspected or overt abnormal bleeding (e.g., appearance of blood in stools or urine, hematuria, excessive menstrual bleeding, melena, petechiae, excessive bruising or persistent oozing from superficial injuries) are early manifestations of anticoagulation beyond a safe and satisfactory level.

Treatment: Excessive anticoagulation, with or without bleeding, may be controlled by discontinuing COUMADIN (Warfarin Sodium) therapy and if necessary, by administration of oral or parenteral vitamin K_1. (Please see recommendations accompanying vitamin K_1 preparations prior to use.)

Such use of vitamin K_1 reduces response to subsequent COUMADIN (Warfarin Sodium) therapy. Patients may return to a pretreatment thrombotic status following the rapid reversal of a prolonged PT/INR. Resumption of COUMADIN (Warfarin Sodium) administration reverses the effect of vitamin K, and a therapeutic PT/INR can again be obtained by careful dosage adjustment. If rapid anticoagulation is indicated, heparin may be preferable for initial therapy.

If minor bleeding progresses to major bleeding, give 5 to 25 mg (rarely up to 50 mg) parenteral vitamin K_1. In emergency situations of severe hemorrhage, clotting factors can be returned to normal by administering 200 to 500 mL of fresh whole blood or fresh frozen plasma, or by giving commercial Factor IX complex.

A risk of hepatitis and other viral diseases is associated with the use of these blood products; Factor IX complex is also associated with an increased risk of thrombosis. Therefore, these preparations should be used only in exceptional or life-threatening bleeding episodes secondary to COUMADIN (Warfarin Sodium) overdosage.

Purified Factor IX preparations should not be used because they cannot increase the levels of prothrombin, Factor VII and Factor X which are also depressed along with the levels of Factor IX as a result of COUMADIN (Warfarin Sodium) treatment. Packed red blood cells may also be given if significant blood loss has occurred. Infusions of blood or plasma should be monitored carefully to avoid precipitating pulmonary edema in elderly patients or patients with heart disease.

DOSAGE AND ADMINISTRATION

The dosage and administration of COUMADIN (Warfarin Sodium) must be individualized for each patient according to the particular patient's PT/INR response to the drug. The dosage should be adjusted based upon the patient's PT/INR. (See **LABORATORY CONTROL** for full discussion on INR.)

Venous Thromboembolism (including pulmonary embolism): Available clinical evidence indicates that an INR of 2.0–3.0 is sufficient for prophylaxis and treatment of venous thromboembolism and minimizes the risk of hemorrhage associated with higher INRs. In patients with risk factors for recurrent venous thromboembolism including venous insufficiency, inherited thrombophilia, idiopathic venous thromboembolism, and a history of thrombotic events, consideration should be given to longer term therapy (Schulman et al, 1995 and Schulman et al, 1997).

Atrial Fibrillation: Five recent clinical trials evaluated the effects of warfarin in patients with non-valvular atrial fibrillation (AF). Meta-analysis findings of these studies revealed that the effects of warfarin in reducing thromboembolic events including stroke were similar at either moderately high INR (2.0–4.5) or low INR (1.4–3.0). There was a significant reduction in minor bleeds at the low INR. Similar data from clinical studies in valvular atrial fibrillation patients are not available. The trials in non-valvular atrial fibrillation support the American College of Chest Physicians' (ACCP) recommendation that an INR of 2.0–3.0 be used for long term warfarin therapy in appropriate AF patients.

Post-Myocardial Infarction: In post-myocardial infarction patients, COUMADIN (Warfarin Sodium) therapy should be initiated early (2–4 weeks post-infarction) and dosage should be adjusted to maintain an INR of 2.5–3.5 long-term. The recommendation is based on the results of the WARIS study in which treatment was initiated 2 to 4 weeks after the infarction. In patients thought to be at an increased risk of bleeding complications or on aspirin therapy, maintenance of COUMADIN (Warfarin Sodium) therapy at the lower end of this INR range is recommended.

Mechanical and Bioprosthetic Heart Valves: In patients with mechanical heart valve(s), long term prophylaxis with warfarin to an INR of 2.5–3.5 is recommended. In patients with bioprosthetic heart valve(s), based on limited data, the American College of Chest Physicians recommends warfarin therapy to an INR of 2.0–3.0 for 12 weeks after valve insertion. In patients with additional risk factors such as atrial fibrillation or prior thromboembolism, consideration should be given for longer term therapy.

Recurrent Systemic Embolism: In cases where the risk of thromboembolism is great, such as in patients with recurrent systemic embolism, a higher INR may be required.

An INR of greater than 4.0 appears to provide no additional therapeutic benefit in most patients and is associated with a higher risk of bleeding.

Initial Dosage: The dosing of COUMADIN (Warfarin Sodium) must be individualized according to patient's sensitivity to the drug as indicated by the PT/INR. Use of a large loading dose may increase the incidence of hemorrhagic and other complications, does not offer more rapid protection against thrombi formation, and is not recommended. Lower initiation and maintenance doses are recommended for elderly and/or debilitated patients and patients with potential to exhibit greater than expected PT/INR response to COUMADIN (Warfarin Sodium) (see **PRECAUTIONS**). Based on limited data, Asian patients may also require lower initiation and maintenance doses of COUMADIN (Warfarin Sodium) (see **CLINICAL PHAR-**

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Coumadin—Cont.

MACOLOGY). It is recommended that COUMADIN (Warfarin Sodium) therapy be initiated with a dose of 2 to 5 mg per day with dosage adjustments based on the results of PT/INR determinations.

Maintenance: Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of Therapy: The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Missed Dose: The anticoagulant effect of COUMADIN (Warfarin Sodium) persists beyond 24 hours. If the patient forgets to take the prescribed dose of COUMADIN (Warfarin Sodium) at the scheduled time, the dose should be taken as soon as possible on the same day. The patient should not take the missed dose by doubling the daily dose to make up for missed doses, but should refer back to his or her physician.

Intravenous Route of Administration: COUMADIN (Warfarin Sodium) for Injection provides an alternate administration route for patients who cannot receive oral drugs. The IV dosages would be the same as those that would be used orally if the patient could take the drug by the oral route. COUMADIN (Warfarin Sodium) for Injection should be administered as a slow bolus injection over 1 to 2 minutes into a peripheral vein. It is not recommended for intramuscular administration. The vial should be reconstituted with 2.7 mL of sterile Water for Injection and inspected for particulate matter and discoloration immediately prior to use. Do not use if either particulate matter and/or discoloration is noted. After reconstitution, COUMADIN (Warfarin Sodium) for Injection is chemically and physically stable for 4 hours at room temperature. It does not contain any antimicrobial preservative and, thus, care must be taken to assure the sterility of the prepared solution. The vial is not recommended for multiple use and unused solution should be discarded.

LABORATORY CONTROL The PT reflects the depression of vitamin K dependent Factors VII, X and II. There are several modifications of the one-stage PT and the physician should become familiar with the specific method used in his laboratory. The degree of anticoagulation indicated by any range of PTs may be altered by the type of thromboplastin used; the appropriate therapeutic range must be based on the experience of each laboratory. The PT should be determined daily after the administration of the initial dose until PT/INR results stabilize in the therapeutic range. Intervals between subsequent PT/INR determinations should be based upon the physician's judgment of the patient's reliability and response to COUMADIN (Warfarin Sodium) in order to maintain the individual within the therapeutic range. Acceptable intervals for PT/INR determinations are normally within the range of one to four weeks after a stable dosage has been determined. To ensure adequate control, it is recommended that additional PT tests are done when other warfarin products are interchanged with warfarin sodium tablets, USP, as well as whenever other medications are initiated, discontinued, or taken irregularly (see **PRECAUTIONS**).

Different thromboplastin reagents vary substantially in their sensitivity to sodium warfarin-induced effects on PT. To define the appropriate therapeutic regimen it is important to be familiar with the sensitivity of the thromboplastin reagent used in the laboratory and its relationship to the International Reference Preparation (IRP), a sensitive thromboplastin reagent prepared from human brain.

A system of standardizing the PT in oral anticoagulant control was introduced by the World Health Organization in 1983. It is based upon the determination of an International Normalized Ratio (INR) which provides a common basis for communication of PT results and interpretations of therapeutic ranges. The INR system of reporting is based on a logarithmic relationship between the PT ratios of the test and reference preparation. The INR is the PT ratio that would be obtained if the International Reference Preparation (IRP), which has an ISI of 1.0, was used to perform the test. Early clinical studies of oral anticoagulants, which formed the basis for recommended therapeutic ranges of 1.5 to 2.5 times control mean normal PT, used sensitive human brain thromboplastin. When using the less sensitive rabbit brain thromboplastins commonly employed in PT assays today, adjustments must be made to the targeted PT range that reflect this decrease in sensitivity.

The INR can be calculated as: INR = (observed PT ratio)^{ISI} where the ISI (International Sensitivity Index) is the correction factor in the equation that relates the PT ratio of the local reagent to the reference preparation and is a measure of the sensitivity of a given thromboplastin to reduction of vitamin K-dependent coagulation factors; the lower the ISI, the more "sensitive" the reagent and the closer the derived INR will be to the observed PT ratio.[1]

The proceedings and recommendations of the 1992 National Conference on Antithrombotic Therapy[2–4] review and evaluate issues related to oral anticoagulant therapy and the sensitivity of thromboplastin reagents and provide additional guidelines for defining the appropriate therapeutic regimen.

The conversion of the INR to PT ratios for the less-intense (INR 2.0–3.0) and more intense (INR 2.5–3.5) therapeutic range recommended by the ACCP for thromboplastins over a range of ISI values is shown in Table 3.[5]

[See table 3 at top of previous page]

TREATMENT DURING DENTISTRY AND SURGERY The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. PT/INR determination is recommended just prior to any dental or surgical procedure. In patients undergoing minimal invasive procedures who must be anticoagulated prior to, during, or immediately following these procedures, adjusting the dosage of COUMADIN (Warfarin Sodium) to maintain the PT/INR at the low end of the therapeutic range may safely allow for continued anticoagulation. The operative site should be sufficiently limited and accessible to permit the effective use of local procedures for hemostasis. Under these conditions, dental and minor surgical procedures may be performed without undue risk of hemorrhage. Some dental or surgical procedures may necessitate the interruption of COUMADIN (Warfarin Sodium) therapy. When discontinuing COUMADIN (Warfarin Sodium) even for a short period of time, the benefits and risks should be strongly considered.

CONVERSION FROM HEPARIN THERAPY Since the anticoagulant effect of COUMADIN (Warfarin Sodium) is delayed, heparin is preferred initially for rapid anticoagulation. Conversion to COUMADIN (Warfarin Sodium) may begin concomitantly with heparin therapy or may be delayed 3 to 6 days. To ensure continuous anticoagulation, it is advisable to continue full dose heparin therapy and that COUMADIN (Warfarin Sodium) therapy be overlapped with heparin for 4 to 5 days, until COUMADIN (Warfarin Sodium) has produced the desired therapeutic response as determined by PT/INR. When COUMADIN (Warfarin Sodium) has produced the desired PT/INR or prothrombin activity, heparin may be discontinued.

COUMADIN (Warfarin Sodium) may increase the aPTT test, even in the absence of heparin. During initial therapy with COUMADIN, the interference with heparin anticoagulation is of minimal clinical significance.

As heparin may affect the PT/INR, patients receiving both heparin and COUMADIN (Warfarin Sodium) should have blood for PT/INR determination drawn at least:

- 5 hours after the last IV bolus dose of heparin, or
- 4 hours after cessation of a continuous IV infusion of heparin, or
- 24 hours after the last subcutaneous heparin injection.

HOW SUPPLIED

Tablets: For oral use, single scored with one face imprinted numerically with 1, 2, 2-1/2, 3, 4, 5, 6, 7-1/2 or 10 superimposed and inscribed with "COUMADIN" and with the opposite face plain. COUMADIN (Warfarin Sodium) is available in bottles and Hospital Unit-Dose Blister Packages with potencies and colors as follows:

[See table below]

Protect from light. Store at controlled room temperature (59°–86°F, 15°–30°C). Dispense in a tight, light-resistant container as defined in the USP.

Hospital Unit-Dose Blister Packages are to be stored in carton until contents have been used.

Injection: Available for intravenous use only. Not recommended for intramuscular administration. Reconstitute with 2.7 mL of sterile Water for Injection to yield 2 mg/mL. Net contents 5.4 mg lyophilized powder. Maximum yield 2.5 mL.

5 mg vial (box of 6) NDC 0590-0324-35

Protect from light. Keep vial in box until used. Store at controlled room temperature (59°–86°F, 15°–30°C).

After reconstitution, store at controlled room temperature (59°–86°F, 15°–30°C) and use within 4 hours. Do not refrigerate. Discard any unused solution.

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	100's	1000's	Hospital Unit-Dose Blister Package of 100
1 mg pink	NDC 0056-0169-70	NDC 0056-0169-90	NDC 0056-0169-75
2 mg lavender	NDC 0056-0170-70	NDC 0056-0170-90	NDC 0056-0170-75
2-1/2 mg green	NDC 0056-0176-70	NDC 0056-0176-90	NDC 0056-0176-75
3 mg tan	NDC 0056-0188-70	NDC 0056-0188-90	NDC 0056-0188-75
4 mg blue	NDC 0056-0168-70	NDC 0056-0168-90	NDC 0056-0168-75
5 mg peach	NDC 0056-0172-70	NDC 0056-0172-90	NDC 0056-0172-75
6 mg teal	NDC 0056-0189-70	NDC 0056-0189-90	NDC 0056-0189-75
7-1/2 mg yellow	NDC 0056-0173-70		NDC 0056-0173-75
10 mg white (Dye Free)	NDC 0056-0174-70		NDC 0056-0174-75

Distributed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 U.S.A.

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6572-01/Rev. June, 2002

Shown in Product Identification Guide, page 310

GLUCOVANCE® ℞

[glēw'kō-văns]

(Glyburide and Metformin HCl Tablets)

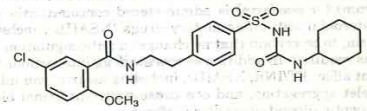
℞ only

1.25 mg/250 mg;
2.5 mg/500 mg;
5 mg/500 mg

DESCRIPTION

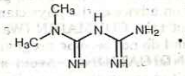
GLUCOVANCE® (Glyburide and Metformin HCl Tablets) contains two oral antihyperglycemic drugs used in the management of type 2 diabetes, glyburide and metformin hydrochloride.

Glyburide is an oral antihyperglycemic drug of the sulfonylurea class. The chemical name for glyburide is 1-[[*p*-[2-(5-chloro-*o*-anisamido)ethyl]phenyl]sulfonyl]-3-cyclohexylurea. Glyburide is a white to off-white crystalline compound with a molecular formula of $C_{23}H_{28}ClN_3O_5S$ and a molecular weight of 494.01. The glyburide used in GLUCOVANCE has a particle size distribution of 25% undersize value not more than 6 µm, 50% undersize value not more than 7-10 µm, and 75% undersize value not more than 21 µm. The structural formula is represented below:



Glyburide

Metformin hydrochloride is an oral antihyperglycemic drug used in the management of type 2 diabetes. Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide monohydrochloride) is not chemically or pharmacologically related to sulfonylureas, thiazolidinediones, or α-glucosidase inhibitors. It is a white to off-white crystalline compound with a molecular formula of $C_4H_{12}ClN_5$ (monohydrochloride) and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula is as shown:



Metformin Hydrochloride

GLUCOVANCE is available for oral administration in tablets containing 1.25 mg glyburide with 250 mg metformin hydrochloride, 2.5 mg glyburide with 500 mg metformin hydrochloride, and 5 mg glyburide with 500 mg metformin hydrochloride. In addition, each tablet contains the following inactive ingredients: microcrystalline cellulose, povidone, croscarmellose sodium, and magnesium stearate. The tablets are film coated, which provides color differentiation.

CLINICAL PHARMACOLOGY

Mechanism of Action

GLUCOVANCE (Glyburide and Metformin HCl Tablets) combines metformin hydrochloride and glyburide, two antihyperglycemic agents with complementary mechanisms of action, to improve glycemic control in patients with type 2 diabetes.

Glyburide appears to lower blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. The mechanism by which glyburide lowers blood glucose during long-term administration has not been clearly established. With chronic administration in patients with type 2

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Cardiovascular: Angina, myocardial infarction (see WARNINGS).
Gastrointestinal: Colonic ischemia (see WARNINGS).
Lower Respiratory: Dyspnea.
Neurologic: Cerebral vascular accident, including transient ischemic attack, subarachnoid hemorrhage, and cerebral infarction (see WARNINGS).
General: Hypersensitivity, including anaphylaxis/anaphylactoid reactions, in some cases severe (e.g., circulatory collapse) (see WARNINGS).

DRUG ABUSE AND DEPENDENCE

In one clinical study enrolling 12 subjects, all of whom had experience using oral opiates and other psychoactive drugs, AMERGE Tablets produced less intense subjective responses ordinarily associated with many drugs of abuse than did codeine (30 to 90 mg).

OVERDOSAGE

A patient who was mildly hypertensive experienced a significant increase in blood pressure after administration of a 10-mg dose starting at 30 minutes (baseline value of 150/98 to 204/144 mmHg 225 minutes). This event resolved after treatment with antihypertensive therapy. Oral administration of 25 mg of naratriptan in 1 healthy young male subject increased blood pressure from 120/67 mmHg pretreatment up to 191/113 mmHg at approximately 6 hours postdose and resulted in adverse events including lightheadedness, tension in the neck, tiredness, and loss of coordination. Blood pressure returned to near baseline by 8 hours after dosing without any pharmacological intervention.
Another subject experienced asymptomatic ischemic ECG changes likely due to coronary artery vasospasm approximately 2 hours following a 7.5-mg oral dose.
The elimination half-life of naratriptan is about 6 hours (see CLINICAL PHARMACOLOGY), and therefore monitoring of patients after overdose with AMERGE Tablets should continue for at least 24 hours or while symptoms or signs persist. There is no specific antidote to naratriptan. Standard supportive treatment should be applied as required. If the patient presents with chest pain or other symptoms consistent with angina pectoris, ECG monitoring should be performed for evidence of ischemia. It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentrations of naratriptan.

DOSAGE AND ADMINISTRATION

In controlled clinical trials, single doses of 1 and 2.5 mg of AMERGE Tablets taken with fluid were effective for the acute treatment of migraines in adults. A greater proportion of patients had headache response following a 2.5-mg dose than following a 1-mg dose (see CLINICAL TRIALS). Individuals may vary in response to doses of AMERGE Tablets. The choice of dose should therefore be made on an individual basis, weighing the possible benefit of the 2.5-mg dose with the potential for a greater risk of adverse events. If the headache returns or if the patient has only partial response, the dose may be repeated once after 4 hours, for a maximum dose of 5 mg in a 24-hour period. There is evidence that doses of 5 mg do not provide a greater effect than 2.5 mg. The safety of treating, on average, more than 4 headaches in a 30-day period has not been established.
Renal Impairment: The use of AMERGE is contraindicated in patients with severe renal impairment (creatinine clearance, <15 mL/min) because of decreased clearance of the drug (see CONTRAINDICATIONS and CLINICAL PHARMACOLOGY). In patients with mild to moderate renal impairment, the maximum daily dose should not exceed 2.5 mg over a 24-hour period and a lower starting dose should be considered.
Hepatic Impairment: The use of AMERGE is contraindicated in patients with severe hepatic impairment (Child-Pugh grade C) because of decreased clearance (see CONTRAINDICATIONS and CLINICAL PHARMACOLOGY). In patients with mild or moderate hepatic impairment, the maximum daily dose should not exceed 2.5 mg over a 24-hour period and a lower starting dose should be considered (see CLINICAL PHARMACOLOGY).

HOW SUPPLIED

AMERGE Tablets 1 and 2.5 mg of naratriptan (base) as the hydrochloride. AMERGE Tablets, 1 mg, are white, D-shaped, film-coated tablets debossed with "GX CE3" on one side in blister packs of 9 tablets (NDC 0173-0561-00).
AMERGE Tablets, 2.5 mg, are green, D-shaped, film-coated tablets debossed with "GX CE5" on one side in blister packs of 9 tablets (NDC 0173-0562-00).
Store at controlled room temperature, 20° to 25°C (68° to 77°F) (see USP).

PATIENT INFORMATION

The following wording is contained in a separate leaflet provided for patients.

Information for the Patient
AMERGE® (naratriptan hydrochloride) Tablets

Please read this leaflet carefully before you take AMERGE Tablets. This leaflet provides a summary of the information available about your medicine. Please do not throw away this leaflet until you have finished your medicine. You may need to read this leaflet again. This leaflet does not contain all the information on AMERGE Tablets. For further information or advice, ask your doctor or pharmacist.

Information About Your Medicine:

The name of your medicine is AMERGE (naratriptan hydrochloride) Tablets. It can be obtained only by prescription from your doctor. The decision to use AMERGE Tablets is one that you and your doctor should make jointly, taking into account your individual preferences and medical circumstances. If you have risk factors for heart disease (such as high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease, or you are postmenopausal or a male over 40), you should tell your doctor, who should evaluate you for heart disease in order to determine if AMERGE is appropriate for you. The majority of those who have taken AMERGE Tablets have not experienced any significant side effects. Rarely, deaths and/or serious heart problems have been reported with this class of medicines; in all but a few instances, however, these deaths and/or serious heart problems occurred in people with heart disease and it was not clear whether these medicines were a contributing factor.

1. The Purpose of Your Medicine:

AMERGE Tablets are intended to relieve your migraine, but not to prevent or reduce the number of attacks you experience. Use AMERGE Tablets only to treat an actual migraine attack.

2. Important Questions to Consider Before Taking AMERGE Tablets:

If the answer to any of the following questions is **YES** or if you do not know the answer, then please discuss it with your doctor before you use AMERGE Tablets.

- Are you pregnant? Do you think you might be pregnant? Are you trying to become pregnant? Are you not using adequate contraception? Are you breastfeeding?
- Do you have any chest pain, heart disease, shortness of breath, or irregular heartbeats? Have you had a heart attack?
- Do you have risk factors for heart disease (such as high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease, or you are postmenopausal or a male over 40)?
- Have you had a stroke, transient ischemic attacks (TIAs), or Raynaud syndrome?
- Do you have high blood pressure?
- Have you ever had to stop taking this or any other medicine because of an allergy or other problems?
- Are you taking any other migraine medicines, including other 5-HT_1 agonists such as IMITREX® (sumatriptan), or medicines containing ergotamine, dihydroergotamine, or methysergide?
- Are you taking any medicine for depression such as selective serotonin reuptake inhibitors (SSRIs)?
- Have you had, or do you have, any disease of the kidney or liver?
- Is this headache different from your usual migraine attacks?

Remember, if you answered **YES** to any of the above questions, then discuss it with your doctor.

3. The Use of AMERGE Tablets During Pregnancy:

Do not use AMERGE Tablets if you are pregnant, think you might be pregnant, are trying to become pregnant, or are not using adequate contraception, unless you have discussed this with your doctor.

4. How to Use AMERGE Tablets:

For adults, the usual dose is a single tablet taken whole with fluids. It may be given at any time after the headache starts. For an individual attack, if you have no response to the first tablet, do not take a second tablet without first talking to your doctor. If you need more relief due to a partial response or return of your headache after the first tablet, a second tablet may be taken but not sooner than 4 hours following the first tablet. Do not take more than a total of 2 AMERGE Tablets in any 24-hour period. If you have kidney or liver disease, take as directed by your doctor.

5. Side Effects to Watch for:

- Some patients experience pain or tightness in the chest or throat when using AMERGE Tablets. If this happens to you, then discuss it with your doctor before using any more AMERGE Tablets. If the chest pain, tightness, or pressure is severe or does not go away, call your doctor immediately.
- If you have sudden and/or severe abdominal pain following AMERGE Tablets, call your doctor immediately.
- Shortness of breath; wheeziness; heart throbbing, swelling of eyelids, face, or lips; or a skin rash, skin lumps, or hives happens rarely. If it happens to you, then tell your doctor immediately. Do not take any more AMERGE Tablets unless your doctor tells you to do so.
- Some people may have feelings of tingling, heat, flushing (redness of face lasting a short time), heaviness or pressure after treatment with AMERGE Tablets. A few people may feel drowsy, dizzy, tired, or sick. Tell your doctor of these symptoms at your next visit.
- If you feel unwell in any other way or have any symptoms that you do not understand, you should contact your doctor immediately.

6. What to Do if an Overdose Is Taken:

If you have taken more medicine than you have been told, contact either your doctor, hospital emergency department, or nearest poison control center immediately.

7. Storing Your Medicine:

Keep your medicine in a safe place where children cannot reach it. It may be harmful to children. Store your medicine away from heat and light. Do not store at temperatures above 77°F (25°C). If your medicine has expired (the expiration date is printed on the treatment pack), throw it away as instructed. If your doctor decides to stop your treatment, do not keep any leftover medicine unless your doctor tells you to. Throw away your medicine as instructed.
GlaxoSmithKline, Research Triangle Park, NC 27709

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May 2003/RL-2007
Shown in Product Identification Guide, page 315

AMOXIL® Rx

[ə-mäx' il]
(amoxicillin capsules, tablets, chewable tablets, and powder for oral suspension)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of AMOXIL (amoxicillin) and other antibacterial drugs, AMOXIL should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Formulations of AMOXIL contain amoxicillin, a semisynthetic antibiotic, an analog of ampicillin, with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. Chemically it is (2*S*,5*R*,6*R*)-6-[(*R*)-(-)-2-amino-2-(*p*-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate.
The amoxicillin molecular formula is $C_{16}H_{19}N_3O_5S \cdot 3H_2O$, and the molecular weight is 419.45.
Capsules, tablets, and powder for oral suspension of AMOXIL are intended for oral administration.
Capsules: Each capsule of AMOXIL, with royal blue opaque cap and pink opaque body, contains 250 mg or 500 mg amoxicillin as the trihydrate. The cap and body of the 250-mg capsule are imprinted with the product name AMOXIL and 250; the cap and body of the 500-mg capsule are imprinted with AMOXIL and 500. Inactive ingredients: D&C Red No. 28, FD&C Blue No. 1, FD&C Red No. 40, gelatin, magnesium stearate, and titanium dioxide.
Tablets: Each tablet contains 500 mg or 875 mg amoxicillin as the trihydrate. Each film-coated, capsule-shaped, pink tablet is debossed with AMOXIL centered over 500 or 875, respectively. The 875-mg tablet is scored on the reverse side. Inactive ingredients: Colloidal silicon dioxide, crospovidone, FD&C Red No. 30 aluminum lake, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide.
Chewable Tablets: Each cherry-banana-peppermint-flavored tablet contains 200 mg or 400 mg amoxicillin as the trihydrate.
Each 200-mg chewable tablet contains 0.0005 mEq (0.0107 mg) of sodium; the 400-mg chewable tablet contains 0.0009 mEq (0.0215 mg) of sodium. The 200-mg and 400-mg pale pink round tablets are imprinted with the product name AMOXIL and 200 or 400 along the edge of 1 side. Inactive ingredients: Aspartame*, crospovidone NF, FD&C Red No. 40 aluminum lake, flavorings, magnesium stearate, and mannitol.
*See **PRECAUTIONS**.
Powder for Oral Suspension: Each 5 mL of reconstituted suspension contains 125 mg, 200 mg, 250 mg, or 400 mg amoxicillin as the trihydrate. Each 5 mL of the 125-mg reconstituted suspension contains 0.11 mEq (2.51 mg) of sodium; each 5 mL of the 250-mg reconstituted suspension contains 0.15 mEq (3.36 mg) of sodium. Each 5 mL of the 200-mg reconstituted suspension contains 0.15 mEq (3.39 mg) of sodium; each 5 mL of the 400-mg reconstituted suspension contains 0.19 mEq (4.33 mg) of sodium.
Pediatric Drops for Oral Suspension: Each mL of reconstituted suspension contains 50 mg amoxicillin as the trihydrate and 0.03 mEq (0.69 mg) of sodium.
Amoxicillin trihydrate for oral suspension 125 mg/5 mL (reconstituted) is a strawberry-flavored pink suspension; the 200 mg/5 mL, 250 mg/5 mL (or 50 mg/mL), and 400 mg/5 mL are bubble-gum-flavored pink suspensions. Inactive ingredients: FD&C Red No. 3, flavorings, silica gel, sodium benzoate, sodium citrate, sucrose, and xanthan gum.

CLINICAL PHARMACOLOGY

Amoxicillin is stable in the presence of gastric acid and is rapidly absorbed after oral administration. The effect of food on the absorption of amoxicillin from the tablets and suspension of AMOXIL has been partially investigated. The 400-mg and 875-mg formulations have been studied only when administered at the start of a light meal. However, food effect studies have not been performed with the 200-mg and 500-mg formulations. Amoxicillin diffuses readily into most body tissues and fluids, with the exception of brain and spinal fluid, except when meninges are inflamed. The half-life of amoxicillin is 61.3 minutes. Most of the amoxicillin is excreted unchanged in the urine; its excretion can be delayed by concurrent administration of probenecid. In blood serum, amoxicillin is approximately 20% protein-bound.

Continued on next page

This product information is based on labeling in effect on August 1, 2003. Further information is available at: GlaxoSmithKline, PO Box 13398, Research Triangle Park, NC 27709. 1-888-825-5249. Corporate Web Site: www.gsk.com

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Amoxil—Cont.

Orally administered doses of 250-mg and 500-mg amoxicillin capsules result in average peak blood levels 1 to 2 hours after administration in the range of 3.5 mcg/mL to 5.0 and 5.5 mcg/mL to 7.5 mcg/mL, respectively.

Mean amoxicillin pharmacokinetic parameters from an open, two-part, single-dose crossover bioequivalence study in 27 adults comparing 875 mg of AMOXIL with 875 mg of AUGMENTIN® (amoxicillin/clavulanate potassium) showed that the 875-mg tablet of AMOXIL produces an $AUC_{0-\infty}$ of 35.4 ±8.1 mcg.hr./mL and a C_{max} of 13.8 ± 4.1 mcg/mL. Dosing was at the start of a light meal following an overnight fast.

Orally administered doses of amoxicillin suspension, 125 mg/5 mL and 250 mg/5 mL, result in average peak blood levels 1 to 2 hours after administration in the range of 1.5 mcg/mL to 3.0 mcg/mL and 3.5 mcg/mL to 5.0 mcg/mL, respectively.

Oral administration of single doses of 400-mg chewable tablets and 400-mg/5 mL suspension of AMOXIL to 24 adult volunteers yielded comparable pharmacokinetic data:

Dose*	$AUC_{0-\infty}$ (mcg.hr./mL)	C_{max} (mcg/mL)†
Amoxicillin		
400 mg (5 mL of suspension)	17.1 (3.1)	5.92 (1.62)
400 mg (one chewable tablet)	17.9 (2.4)	5.18 (1.64)

* Administered at the start of a light meal.
† Mean values of 24 normal volunteers. Peak concentrations occurred approximately 1 hour after the dose.

Detectable serum levels are observed up to 8 hours after an orally administered dose of amoxicillin. Following a 1-gram dose and utilizing a special skin window technique to determine levels of the antibiotic, it was noted that therapeutic levels were found in the interstitial fluid. Approximately 60% of an orally administered dose of amoxicillin is excreted in the urine within 6 to 8 hours.

Microbiology: Amoxicillin is similar to ampicillin in its bactericidal action against susceptible organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. Amoxicillin has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Aerobic gram-positive microorganisms:
Enterococcus faecalis
Staphylococcus spp.* (β-lactamase-negative strains only)
Streptococcus pneumoniae
Streptococcus spp. (α- and β-hemolytic strains only)

* Staphylococci which are susceptible to amoxicillin but resistant to methicillin/oxacillin should be considered as resistant to amoxicillin.

Aerobic gram-negative microorganisms:
Escherichia coli (β-lactamase-negative strains only)
Haemophilus influenzae (β-lactamase-negative strains only)
Neisseria gonorrhoeae (β-lactamase-negative strains only)
Proteus mirabilis (β-lactamase-negative strains only)

Helicobacter:
Helicobacter pylori

Susceptibility tests: ***Dilution techniques:*** Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of **ampicillin** powder. Ampicillin is sometimes used to predict susceptibility of *S. pneumoniae* to amoxicillin; however, some intermediate strains have been shown to be susceptible to amoxicillin. Therefore, *S. pneumoniae* susceptibility should be tested using amoxicillin powder. The MIC values should be interpreted according to the following criteria:

For gram-positive aerobes:
Enterococcus

MIC (mcg/mL)	Interpretation
≤8	Susceptible (S)
≥16	Resistant (R)

Staphylococcus[a]

MIC (mcg/mL)	Interpretation
≤0.25	Susceptible (S)
≥0.5	Resistant (R)

Streptococcus (except *S. pneumoniae*)

MIC (mcg/mL)	Interpretation
≤0.25	Susceptible (S)
0.5 to 4	Intermediate (I)
≥8	Resistant (R)

S. pneumoniae[b] from non-meningitis sources.
(**Amoxicillin** powder should be used to determine susceptibility.)

MIC (mcg/mL)	Interpretation
≤2.0	Susceptible (S)
4.0	Intermediate (I)
≥8.0	Resistant (R)

Note: These interpretive criteria are based on the recommended doses for respiratory tract infections.

For gram-negative aerobes:
Enterobacteriaceae

MIC (mcg/mL)	Interpretation
≤8	Susceptible (S)
16	Intermediate (I)
≥32	Resistant (R)

H. influenzae[c]

MIC (mcg/mL)	Interpretation
≤1	Susceptible (S)
2	Intermediate (I)
≥4	Resistant (R)

a. Staphylococci which are susceptible to amoxicillin but resistant to methicillin/oxacillin should be considered as resistant to amoxicillin.
b. These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.
c. These interpretive standards are applicable only to broth microdilution test with *H. influenzae* using *Haemophilus* Test Medium (HTM).[1]

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard **ampicillin** powder should provide the following MIC values:

Microorganism		MIC (mcg/mL)
E. coli	ATCC 25922	2 to 8
E. faecalis	ATCC 29212	0.5 to 2
H. influenzae	ATCC 49247[d]	2 to 8
S. aureus	ATCC 29213	0.25 to 1

Using **amoxicillin** to determine susceptibility:

Microorganism		MIC Range (mcg/mL)
S. pneumoniae	ATCC 49619[e]	0.03 to 0.12

d. This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using HTM.[1]
e. This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by the broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

Diffusion techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10 mcg ampicillin to test the susceptibility of microorganisms, except *S. pneumoniae,* , to amoxicillin. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for **ampicillin.**

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 10-mcg ampicillin disk should be interpreted according to the following criteria:

For gram-positive aerobes:
Enterococcus

Zone Diameter (mm)	Interpretation
≥17	Susceptible (S)
≤16	Resistant (R)

Staphylococcus[f]

Zone Diameter (mm)	Interpretation
≥29	Susceptible (S)
≤28	Resistant (R)

β-hemolytic streptococci

Zone Diameter (mm)	Interpretation
≥26	Susceptible (S)
19 to 25	Intermediate (I)
≤18	Resistant (R)

NOTE: For streptococci (other than β-hemolytic streptococci and *S. pneumoniae*), an ampicillin MIC should be determined.

S. pneumoniae

S. pneumoniae should be tested using a 1-mcg oxacillin disk. Isolates with oxacillin zone sizes of ≥20 mm are susceptible to amoxicillin. An amoxicillin MIC should be determined on isolates of *S. pneumoniae* with oxacillin zone sizes of ≤19 mm.

For gram-negative aerobes:
Enterobacteriaceae

Zone Diameter (mm)	Interpretation
≥17	Susceptible (S)
14 to 16	Intermediate (I)
≤13	Resistant (R)

H. influenzae[g]

Zone Diameter (mm)	Interpretation
≥22	Susceptible (S)
19 to 21	Intermediate (I)
≤18	Resistant (R)

f. Staphylococci which are susceptible to amoxicillin but resistant to methicillin/oxacillin should be considered as resistant to amoxicillin.
g. These interpretive standards are applicable only to disk diffusion susceptibility tests with *H. influenzae* using *Haemophilus* Test Medium (HTM).[2]

Interpretation should be as stated above for results using dilution techniques.

As with standard dilution techniques, disk diffusion susceptibility test procedures require the use of laboratory control microorganisms. The 10-mcg **ampicillin** disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism		Zone diameter (mm)
E. coli	ATCC 25922	16 to 22
H. influenzae	ATCC 49247[h]	13 to 21
S. aureus	ATCC 25923	27 to 35

Using 1-mcg **oxacillin** disk:

Microorganism		Zone diameter (mm)
S. pneumoniae	ATCC 49619[i]	8 to 12

h. This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a disk diffusion procedure using HTM.[2]
i. This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a disk diffusion procedure using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2.

Susceptibility testing for *Helicobacter pylori:* In vitro susceptibility testing methods and diagnostic products currently available for determining minimum inhibitory concentrations (MICs) and zone sizes have not been standardized, validated, or approved for testing *H. pylori* microorganisms.

Culture and susceptibility testing should be obtained in patients who fail triple therapy. If clarithromycin resistance is found, a non-clarithromycin-containing regimen should be used.

INDICATIONS AND USAGE

AMOXIL is indicated in the treatment of infections due to susceptible (ONLY β-lactamase-negative) strains of the designated microorganisms in the conditions listed below:

Infections of the ear, nose, and throat due to *Streptococcus* spp. (α- and β-hemolytic strains only), *S. pneumoniae, Staphylococcus* spp., or *H. influenzae*

Infections of the genitourinary tract due to *E. coli, P. mirabilis,* or *E. faecalis*

Infections of the skin and skin structure due to *Streptococcus* spp. (α- and β-hemolytic strains only), *Staphylococcus* spp., or *E. coli.*

Infections of the lower respiratory tract due to *Streptococcus* spp. (α- and β-hemolytic strains only), *S. pneumoniae, Staphylococcus* spp., or *H. influenzae.*

Gonorrhea, acute uncomplicated (ano-genital and urethral infections) due to *N. gonorrhoeae* (males and females).

H. pylori eradication to reduce the risk of duodenal ulcer recurrence

Triple therapy: AMOXIL/clarithromycin/lansoprazole

AMOXIL, in combination with clarithromycin plus lansoprazole as triple therapy, is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. (See CLINICAL STUDIES and DOSAGE AND ADMINISTRATION.)

Dual therapy: AMOXIL/lansoprazole

AMOXIL, in combination with lansoprazole delayed-release capsules as dual therapy, is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or 1-year history of a duodenal ulcer) **who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected.** (See the clarithromycin package insert, MICROBIOLOGY.) Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. (See CLINICAL STUDIES and DOSAGE AND ADMINISTRATION.)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of AMOXIL and other antibacterial drugs, AMOXIL should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy. Indicated surgical procedures should be performed.

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CONTRAINDICATIONS

A history of allergic reaction to any of the penicillins is a contraindication.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH AMOXIL, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AMOXIL SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including amoxicillin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate-to-severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS

General: The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur, amoxicillin should be discontinued and appropriate therapy instituted.

Prescribing AMOXIL in the absence of proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Phenylketonurics: Each 200-mg chewable tablet of AMOXIL contains 1.82 mg phenylalanine; each 400-mg chewable tablet contains 3.64 mg phenylalanine. The suspensions of AMOXIL do not contain phenylalanine and can be used by phenylketonurics.

Laboratory Tests: As with any potent drug, periodic assessment of renal, hepatic, and hematopoietic function should be made during prolonged therapy.

All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis. Patients treated with amoxicillin should have a follow-up serologic test for syphilis after 3 months.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use of amoxicillin and probenecid may result in increased and prolonged blood levels of amoxicillin.

Chloramphenicol, macrolides, sulfonamides, and tetracyclines may interfere with the bactericidal effects of penicillin. This has been demonstrated in vitro however, the clinical significance of this interaction is not well documented.

Drug/Laboratory Test Interactions: High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using Clinitest®, Benedict's Solution or Fehling's Solution. Since this effect may also occur with amoxicillin, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as CLINISTIX®) be used.

Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with amoxicillin.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential. Studies to detect mutagenic potential of amoxicillin alone have not been conducted; however, the following information is available from tests on a 4:1 mixture of amoxicillin and potassium clavulanate (AUGMENTIN). AUGMENTIN was non-mutagenic in the Ames bacterial mutation assay, and the yeast gene conversion assay. AUGMENTIN was weakly positive in the mouse lymphoma assay, but the trend toward increased mutation frequencies in this assay occurred at doses that were also associated with decreased cell survival. AUGMENTIN was negative in the mouse micronucleus test, and in the dominant lethal assay in mice. Potassium clavulanate alone was tested in the Ames bacterial mutation assay and in the mouse micronucleus test, and was negative in each of these assays. In a multi-generation reproduction study in rats, no impairment of fertility or other adverse reproductive effects were seen at doses up to 500 mg/kg (approximately 3 times the human dose in mg/m^2).

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category B. Reproduction studies have been performed in mice and rats at doses up to 10 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to amoxicillin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Oral ampicillin-class antibiotics are poorly absorbed during labor. Studies in guinea pigs showed that intravenous administration of ampicillin slightly decreased the uterine tone and frequency of contractions but moderately increased the height and duration of contractions. However, it is not known whether use of amoxicillin in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Penicillins have been shown to be excreted in human milk. Amoxicillin use by nursing mothers may lead to sensitization of infants. Caution should be exercised when amoxicillin is administered to a nursing woman.

Pediatric Use: Because of incompletely developed renal function in neonates and young infants, the elimination of amoxicillin may be delayed. Dosing of AMOXIL should be modified in pediatric patients 12 weeks or younger (≤3 months). (See DOSAGE AND ADMINISTRATION—Neonates and infants.)

Information for Patients: AMOXIL may be taken every 8 hours or every 12 hours, depending on the strength of the product prescribed.

Patients should be counseled that antibacterial drugs, including AMOXIL, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When AMOXIL is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by AMOXIL or other antibacterial drugs in the future.

Adults and pediatric patients >3 months

Infection	Severity*	Usual Adult Dose	Usual Dose for Children >3 months†‡
Ear/nose/throat	Mild/Moderate	500 mg every 12 hours or 250 mg every 8 hours	25 mg/kg/day in divided doses every 12 hours **or** 20 mg/kg/day in divided doses every 8 hours
	Severe	875 mg every 12 hours or 500 mg every 8 hours	45 mg/kg/day in divided doses every 12 hours **or** 40 mg/kg/day in divided doses every 8 hours
Lower respiratory tract	Mild/Moderate or Severe	875 mg every 12 hours or 500 mg every 8 hours	45 mg/kg/day in divided doses every 12 hours **or** 40 mg/kg/day in divided doses every 8 hours
Skin/skin structure	Mild/Moderate	500 mg every 12 hours or 250 mg every 8 hours	25 mg/kg/day in divided doses every 12 hours **or** 20 mg/kg/day in divided doses every 8 hours
	Severe	875 mg every 12 hours or 500 mg every 8 hours	45 mg/kg/day in divided doses every 12 hours **or** 40 mg/kg/day in divided doses every 8 hours
Genitourinary tract	Mild/Moderate	500 mg every 12 hours or 250 mg every 8 hours	25 mg/kg/day in divided doses every 12 hours **or** 20 mg/kg/day in divided doses every 8 hours
	Severe	875 mg every 12 hours or 500 mg every 8 hours	45 mg/kg/day in divided doses every 12 hours **or** 40 mg/kg/day in divided doses every 8 hours
Gonorrhea Acute, uncomplicated ano-genital, and urethral infections in males and females		3 grams as single oral dose	Prepubertal children: 50 mg/kg AMOXIL, combined with 25 mg/kg probenecid as a single dose. **NOTE: SINCE PROBENECID IS CONTRAINDICATED IN CHILDREN UNDER 2 YEARS, DO NOT USE THIS REGIMEN IN THESE CASES.**

* Dosing for infections caused by less susceptible organisms should follow the recommendations for severe infections.

† The children's dosage is intended for individuals whose weight is less than 40 kg. Children weighing 40 kg or more should be dosed according to the adult recommendations.

‡ Each strength of the suspension of AMOXIL is available as a chewable tablet for use by older children.

ADVERSE REACTIONS

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria. The following adverse reactions have been reported as associated with the use of penicillins:

Gastrointestinal: Nausea, vomiting, diarrhea, and hemorrhagic/pseudomembranous colitis.

Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See WARNINGS.)

Hypersensitivity Reactions: Serum sickness like reactions, erythematous maculopapular rashes, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, hypersensitivity vasculitis and urticaria have been reported.

NOTE: These hypersensitivity reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, amoxicillin should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to amoxicillin therapy.

Continued on next page

This product information is based on labeling in effect on August 1, 2003. Further information is available at: GlaxoSmithKline, PO Box 13398, Research Triangle Park, NC 27709. 1-888-825-5249. Corporate Web Site: www.gsk.com

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Amoxil—Cont.

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted, but the significance of this finding is unknown. Hepatic dysfunction including cholestatic jaundice, hepatic cholestasis and acute cytolytic hepatitis have been reported.

Hemic and Lymphatic Systems: Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, convulsions, behavioral changes, and/or dizziness have been reported rarely.

Miscellaneous: Tooth discoloration (brown, yellow, or gray staining) has been rarely reported. Most reports occurred in pediatric patients. Discoloration was reduced or eliminated with brushing or dental cleaning in most cases.

Combination therapy with clarithromycin and lansoprazole:

In clinical trials using combination therapy with amoxicillin plus clarithromycin and lansoprazole, and amoxicillin plus lansoprazole, no adverse reactions peculiar to these drug combinations were observed. Adverse reactions that have occurred have been limited to those that had been previously reported with amoxicillin, clarithromycin, or lansoprazole.

Triple therapy: ***Triple therapy: amoxicillin/clarithromycin/lansoprazole:***

The most frequently reported adverse events for patients who received triple therapy were diarrhea (7%), headache (6%), and taste perversion (5%). No treatment-emergent adverse events were observed at significantly higher rates with triple therapy than with any dual therapy regimen.

Dual therapy: ***Dual therapy: amoxicillin/lansoprazole:***

The most frequently reported adverse events for patients who received amoxicillin 3 times daily plus lansoprazole 3 times daily dual therapy were diarrhea (8%) and headache (7%). No treatment-emergent adverse events were observed at significantly higher rates with amoxicillin 3 times daily plus lansoprazole 3 times daily dual therapy than with lansoprazole alone.

For more information on adverse reactions with clarithromycin or lansoprazole, refer to their package inserts, ADVERSE REACTIONS.

OVERDOSAGE

In case of overdosage, discontinue medication, treat symptomatically, and institute supportive measures as required. If the overdosage is very recent and there is no contraindication, an attempt at emesis or other means of removal of drug from the stomach may be performed. A prospective study of 51 pediatric patients at a poison-control center suggested that overdosages of less than 250 mg/kg of amoxicillin are not associated with significant clinical symptoms and do not require gastric emptying.[3]

Interstitial nephritis resulting in oliguric renal failure has been reported in a small number of patients after overdosage with amoxicillin. Renal impairment appears to be reversible with cessation of drug administration. High blood levels may occur more readily in patients with impaired renal function because of decreased renal clearance of amoxicillin. Amoxicillin may be removed from circulation by hemodialysis.

DOSAGE AND ADMINISTRATION

Capsules, chewable tablets, and oral suspensions of AMOXIL may be given without regard to meals. The 400-mg suspension, 400-mg chewable tablet, and the 875-mg tablet, have been studied only when administered at the start of a light meal. However, food effect studies have not been performed with the 200-mg and 500-mg formulations.

Neonates and infants aged ≤12 weeks (≤3 months): Due to incompletely developed renal function affecting elimination of amoxicillin in this age group, the recommended upper dose of AMOXIL is 30 mg/kg/day divided q12h.

[See table at top of previous page]

After reconstitution, the required amount of suspension should be placed directly on the child's tongue for swallowing. Alternate means of administration are to add the required amount of suspension to formula, milk, fruit juice, water, ginger ale, or cold drinks. These preparations should then be taken immediately. To be certain the child is receiving full dosage, such preparations should be consumed in entirety.

All patients with gonorrhea should be evaluated for syphilis. (See PRECAUTIONS – Laboratory Tests.)

Larger doses may be required for stubborn or severe infections.

General: It should be recognized that in the treatment of chronic urinary tract infections, frequent bacteriological and clinical appraisals are necessary. Smaller doses than those recommended above should not be used. Even higher doses may be needed at times. In stubborn infections, therapy may be required for several weeks. It may be necessary to continue clinical and/or bacteriological follow-up for several months after cessation of therapy. Except for gonorrhea, treatment should be continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. It is recommended that there be at least 10 days' treatment for any infection caused by *Streptococcus pyogenes* to prevent the occurrence of acute rheumatic fever.

H. pylori **eradication to reduce the risk of duodenal ulcer recurrence:** ***Triple therapy:***

AMOXIL/clarithromycin/lansoprazole

The recommended adult oral dose is 1 gram AMOXIL, 500 mg clarithromycin, and 30 mg lansoprazole, all given twice daily (q12h) for 14 days. (See INDICATIONS AND USAGE.)

Dual therapy: AMOXIL/*lansoprazole*

The recommended adult oral dose is 1 gram AMOXIL and 30 mg lansoprazole, each given 3 times daily (q8h) for 14 days. (See INDICATIONS AND USAGE.)

Please refer to clarithromycin and lansoprazole full prescribing information for CONTRAINDICATIONS and WARNINGS, and for information regarding dosing in elderly and renally impaired patients.

Dosing recommendations for adults with impaired renal function: Patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe. Severely impaired patients with a glomerular filtration rate of <30 mL/minute should not receive the 875-mg tablet. Patients with a glomerular filtration rate of 10 to 30 mL/minute should receive 500 mg or 250 mg every 12 hours, depending on the severity of the infection. Patients with a less than 10 mL/minute glomerular filtration rate should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection.

Hemodialysis patients should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection. They should receive an additional dose both during and at the end of dialysis.

There are currently no dosing recommendations for pediatric patients with impaired renal function.

Directions For Mixing Oral Suspension: Prepare suspension at time of dispensing as follows: Tap bottle until all powder flows freely. Add approximately 1/3 of the total amount of water for reconstitution (see table below) and shake vigorously to wet powder. Add remainder of the water and again shake vigorously.

125 mg/5 mL	Amount of Water
Bottle Size	Required for Reconstitution
150 mL	116 mL

Each teaspoonful (5 mL) will contain 125 mg amoxicillin.

200 mg/5 mL	Amount of Water
Bottle Size	Required for Reconstitution
50 mL	39 mL
75 mL	57 mL
100 mL	76 mL

Each teaspoonful (5 mL) will contain 200 mg amoxicillin.

250 mg/5 mL	Amount of Water
Bottle Size	Required for Reconstitution
100 mL	74 mL
150 mL	111 mL

Each teaspoonful (5 mL) will contain 250 mg amoxicillin.

400 mg/5 mL	Amount of Water
Bottle Size	Required for Reconstitution
50 mL	36 mL
75 mL	54 mL
100 mL	71 mL

Each teaspoonful (5 mL) will contain 400 mg amoxicillin.

Directions For Mixing Pediatric Drops: Prepare pediatric drops at time of dispensing as follows: Add the required amount of water (see table below) to the bottle and shake vigorously. Each mL of suspension will then contain amoxicillin trihydrate equivalent to 50 mg amoxicillin.

Bottle Size	Amount of Water Required for Reconstitution
15 mL	12 mL
30 mL	23 mL

NOTE: SHAKE BOTH ORAL SUSPENSION AND PEDIATRIC DROPS WELL BEFORE USING. Keep bottle tightly closed. Any unused portion of the reconstituted suspension must be discarded after 14 days. Refrigeration preferable, but not required.

HOW SUPPLIED

Capsules of AMOXIL. Each capsule contains 250 mg or 500 mg amoxicillin as the trihydrate.

250-mg Capsule	
NDC 0029-6006-32	bottles of 500
500-mg Capsule	
NDC 0029-6007-32	bottles of 500

Tablets of AMOXIL. Each tablet contains 500 mg or 875 mg amoxicillin as the trihydrate.

500-mg Tablet	
NDC 0029-6046-12	bottles of 20
NDC 0029-6046-20	bottles of 100
NDC 0029-6046-25	bottles of 500
875-mg Tablet	
NDC 0029-6047-12	bottles of 20
NDC 0029-6047-20	bottles of 100
NDC 0029-6047-25	bottles of 500

Chewable Tablets of AMOXIL. Each cherry-banana-peppermint-flavored tablet contains 200 mg or 400 mg amoxicillin as the trihydrate.

200-mg Tablet	
NDC 0029-6044-12	bottles of 20
NDC 0029-6044-20	bottles of 100
400-mg Tablet	
NDC 0029-6045-12	bottles of 20
NDC 0029-6045-20	bottles of 100

AMOXIL for Oral Suspension. Each 5 mL of reconstituted strawberry-flavored suspension contains 125 mg amoxicillin as the trihydrate. Each 5 mL of reconstituted bubble-gum-flavored suspension contains 200, 250, or 400 mg amoxicillin as the trihydrate.

125 mg/5 mL	
NDC 0029-6008-22	150-mL bottle
200 mg/5 mL	
NDC 0029-6048-54	50-mL bottle
NDC 0029-6048-55	75-mL bottle
NDC 0029-6048-59	100-mL bottle
250 mg/5 mL	
NDC 0029-6009-23	100-mL bottle
NDC 0029-6009-22	150-mL bottle
400 mg/5 mL	
NDC 0029-6049-54	50-mL bottle
NDC 0029-6049-55	75-mL bottle
NDC 0029-6049-59	100-mL bottle

Pediatric Drops of AMOXIL for Oral Suspension. Each mL of bubble-gum-flavored reconstituted suspension contains 50 mg amoxicillin as the trihydrate.

NDC 0029-6035-20	15-mL bottle
NDC 0029-6038-39	30-mL bottle

Store at or below 20°C (68°F)

- 250-mg and 500-mg capsules
- 125-mg and 250-mg unreconstituted powder

Store at or below 25°C (77°F)

- 200-mg and 400-mg unreconstituted powder
- 200-mg and 400-mg chewable tablets
- 500-mg and 875-mg tablets

Dispense in tight container.

CLINICAL STUDIES

H. pylori eradication to reduce the risk of duodenal ulcer recurrence

H. pylori **eradication to reduce the risk of duodenal ulcer recurrence:** Randomized, double-blind clinical studies performed in the United States in patients with *H. pylori* and duodenal ulcer disease (defined as an active ulcer or history of an ulcer within 1 year) evaluated the efficacy of lansoprazole in combination with amoxicillin capsules and clarithromycin tablets as triple 14-day therapy, or in combination with amoxicillin capsules as dual 14-day therapy, for the eradication of *H. pylori*. Based on the results of these studies, the safety and efficacy of 2 different eradication regimens were established:

Triple therapy: Amoxicillin 1 gram twice daily/clarithromycin 500 mg twice daily/lansoprazole 30 mg twice daily.

Dual therapy: Amoxicillin 1 gram 3 times daily/lansoprazole 30 mg 3 times daily.

All treatments were for 14 days. *H. pylori* eradication was defined as 2 negative tests (culture and histology) at 4 to 6 weeks following the end of treatment.

Triple therapy was shown to be more effective than all possible dual therapy combinations. Dual therapy was shown to be more effective than both monotherapies. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

H. pylori **Eradication Rates—Triple Therapy (amoxicillin/clarithromycin/lansoprazole) Percent of Patients Cured [95% Confidence Interval] (Number of Patients)**

Study	Triple Therapy	Triple Therapy
	Evaluable Analysis*	Intent-to-Treat Analysis†
Study 1	92‡ [80.0–97.7] (n=48)	86‡ [73.3–93.5] (n=55)
Study 2	86§ [75.7–93.6] (n=66)	83§ [72.0–90.8] (n=70)

* This analysis was based on evaluable patients with confirmed duodenal ulcer (active or within 1 year) and *H. pylori* infection at baseline defined as at least 2 of 3 positive endoscopic tests from CLOtest®, (Delta West Ltd., Bentley, Australia), histology, and/or culture. Patients were included in the analysis if they completed the study. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the analysis as failures of therapy.

† Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined above and had a confirmed duodenal ulcer (active or within 1 year). All dropouts were included as failures of therapy.

‡ ($p<0.05$) versus lansoprazole/amoxicillin and lansoprazole/clarithromycin dual therapy.

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‡ ($p<0.05$) versus clarithromycin/amoxicillin dual therapy.

***H. pylori* Eradication Rates—Dual Therapy (amoxicillin/lansoprazole) Percent of Patients Cured [95% Confidence Interval] (Number of Patients)**

Study	Dual Therapy	Dual Therapy
	Evaluable Analysis*	Intent-to-Treat Analysis†
Study 1	77‡‡ [62.5–87.2] (n=51)	70‡‡ [56.8–81.2] (n=60)
Study 2	66§§ [51.9–77.5] (n=58)	61§§ [48.5–72.9] (n=67)

* This analysis was based on evaluable patients with confirmed duodenal ulcer (active or within 1 year) and *H. pylori* infection at baseline defined as at least 2 of 3 positive endoscopic tests from CLOtest®, histology and/or culture. Patients were included in the analysis if they completed the study. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the analysis as failures of therapy.

† Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined above and had a confirmed duodenal ulcer (active or within 1 year). All dropouts were included as failures of therapy.

‡‡ ($p<0.05$) versus lansoprazole alone.

§§ ($p<0.05$) versus lansoprazole alone or amoxicillin alone.

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May 2003/AM:L23

Shown in Product Identification Guide, pages 315, 316

ARGATROBAN

℞

[är-ga' trō-ban]

Injection

DESCRIPTION

Argatroban is a synthetic direct thrombin inhibitor derived from L-arginine. The chemical name for Argatroban is 1-[5-[(aminoiminomethyl)amino]-1-oxo-2-[[(1,2,3,4-tetrahydro-3-methyl-8-quinolinyl)sulfonyl]amino]pentyl]-4-methyl-2-piperidinecarboxylic acid, monohydrate. Argatroban has 4 asymmetric carbons. One of the asymmetric carbons has an *R* configuration (stereoisomer Type I) and an *S* configuration (stereoisomer Type II). Argatroban consists of a mixture of *R* and *S* stereoisomers at a ratio of approximately 65:35.

The molecular formula of Argatroban is $C_{23}H_{36}N_6O_5S \cdot H_2O$. Its molecular weight is 526.66.

Argatroban is a white, odorless crystalline powder that is freely soluble in glacial acetic acid, slightly soluble in ethanol, and insoluble in acetone, ethyl acetate, and ether. Argatroban Injection is a sterile clear, colorless to pale yellow, slightly viscous solution. Argatroban is available in 250-mg (in 2.5-mL) single-use amber vials, with gray flip-top caps. Each mL of sterile, nonpyrogenic solution contains 100 mg Argatroban. Inert ingredients: 750 mg D-sorbitol, 1,000 mg dehydrated alcohol.

CLINICAL PHARMACOLOGY

Mechanism of Action: Argatroban is a direct thrombin inhibitor that reversibly binds to the thrombin active site. Argatroban does not require the co-factor antithrombin III for antithrombotic activity. Argatroban exerts its anticoagulant effects by inhibiting thrombin-catalyzed or -induced reactions, including fibrin formation; activation of coagulation factors V, VIII, and XIII; activation of protein C; and platelet aggregation.

Argatroban is highly selective for thrombin with an inhibitory constant (K_i) of 0.04 μM. At therapeutic concentrations, Argatroban has little or no effect on related serine proteases (trypsin, factor Xa, plasmin, and kallikrein).

Argatroban is capable of inhibiting the action of both free and clot-associated thrombin.

Argatroban does not interact with heparin-induced antibodies. Evaluation of sera in 12 healthy subjects and 8 patients who received multiple doses of Argatroban did not reveal antibody formation to Argatroban (see CLINICAL STUDIES).

Pharmacokinetics: ***Distribution:*** Argatroban distributes mainly in the extracellular fluid as evidenced by an apparent steady-state volume of distribution of 174 mL/kg (12.18 L in a 70-kg adult). Argatroban is 54% bound to human serum proteins, with binding to albumin and α_1-acid glycoprotein being 20% and 34%, respectively.

Metabolism: The main route of Argatroban metabolism is hydroxylation and aromatization of the 3-methyltetrahydroquinoline ring in the liver. The formation of each of the 4 known metabolites is catalyzed *in vitro* by the human liver microsomal cytochrome P450 enzymes CYP3A4/5. The primary metabolite (M1) exerts 3- to 5-fold weaker anticoagulant effects than Argatroban. Unchanged Argatroban is the major component in plasma. The plasma concentrations of M1 range between 0% and 20% of that of the parent drug. The other metabolites (M2 to M4) are found only in very low quantities in the urine and have not been detected in plasma or feces. These data, together with the lack of effect of erythromycin (a potent CYP3A4/5 inhibitor) on Argatroban pharmacokinetics, suggest that CYP3A4/5-mediated metabolism is not an important elimination pathway in vivo.

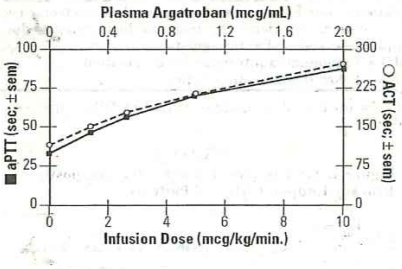
Total body clearance is approximately 5.1 mL/kg/min (0.31 L/kg/hr) for infusion doses up to 40 mcg/kg/min. The terminal elimination half-life of Argatroban ranges between 39 and 51 minutes.

There is no interconversion of the 21–(R):21–(S) diastereoisomers. The plasma ratio of these diastereoisomers is unchanged by metabolism or hepatic impairment, remaining constant at 65:35 (±2%).

Excretion: Argatroban is excreted primarily in the feces, presumably through biliary secretion. In a study in which ^{14}C-Argatroban (5 mcg/kg/min) was infused for 4 hours into healthy subjects, approximately 65% of the radioactivity was recovered in the feces within 6 days of the start of infusion with little or no radioactivity subsequently detected. Approximately 22% of the radioactivity appeared in the urine within 12 hours of the start of infusion. Little or no additional urinary radioactivity was subsequently detected. Average percent recovery of unchanged drug, relative to total dose, was 16% in urine and at least 14% in feces.

Pharmacokinetic/Pharmacodynamic Relationship: When Argatroban is administered by continuous infusion, anticoagulant effects and plasma concentrations of Argatroban follow similar, predictable temporal response profiles, with low intersubject variability. Immediately upon initiation of Argatroban infusion, anticoagulant effects are produced as plasma Argatroban concentrations begin to rise. Steady-state levels of both drug and anticoagulant effect are typically attained within 1 to 3 hours and are maintained until the infusion is discontinued or the dosage adjusted. Steady-state plasma Argatroban concentrations increase proportionally with dose (for infusion doses up to 40 mcg/kg/min in healthy subjects) and are well correlated with steady-state anticoagulant effects. For infusion doses up to 40 mcg/kg/min, Argatroban increases in a dose-dependent fashion, the activated partial thromboplastin time (aPTT), the activated clotting time (ACT), the prothrombin time (PT), the International Normalized Ratio (INR), and the thrombin time (TT) in healthy volunteers and cardiac patients. Representative steady-state plasma Argatroban concentrations and anticoagulant effects are shown below for Argatroban infusion doses up to 10 mcg/kg/min (see Figure 1).

Figure 1. Relationship at Steady State Between Argatroban Dose, Plasma Argatroban Concentration and Anticoagulant Effect



Effect on International Normalized Ratio (INR): Because Argatroban is a direct thrombin inhibitor, co-administration of Argatroban and warfarin produces a combined effect on the laboratory measurement of the INR. However, concurrent therapy, compared to warfarin monotherapy, exerts no additional effect on vitamin K-dependent factor Xa activity. The relationship between INR on co-therapy and warfarin alone is dependent on both the dose of Argatroban and the thromboplastin reagent used. This relationship is influenced by the International Sensitivity Index (ISI) of the thromboplastin. Data for 2 commonly utilized thromboplastins with ISI values of 0.88 (Innovin, Dade) and 1.78 (Thromboplastin C Plus, Dade) are presented in Figure 2 for an Argatroban dose of 2 mcg/kg/min. Thromboplastins with higher ISI values than shown result in higher INRs on combined therapy of warfarin and Argatroban. These data are based on results obtained in normal individuals (see DOSAGE AND ADMINISTRATION, Conversion to Oral Anticoagulant Therapy).

Figure 2. INR Relationship of Argatroban Plus Warfarin Versus Warfarin Alone

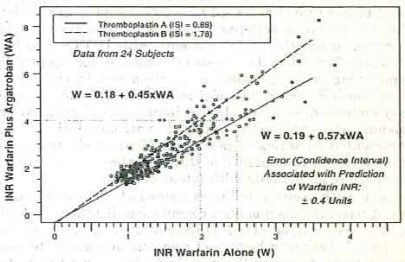


Figure 2 demonstrates the relationship between INR for warfarin alone and INR for warfarin co-administered with Argatroban at a dose of 2 mcg/kg/min. To calculate INR for warfarin alone (INR_W), based on INR for co-therapy of warfarin and Argatroban (INR_{WA}), when the Argatroban dose is 2 mcg/kg/min, use the equation next to the appropriate curve. Example: At a dose of 2 mcg/kg/min and an INR performed with Thromboplastin A, the equation 0.19 + 0.57 (INR_{WA}) = INR_W would allow a prediction of the INR on warfarin alone (INR_W). Thus, using an INR_{WA} value of 4.0 obtained on combined therapy: $INR_W = 0.19 + 0.57\ (4) = 2.47$ as the value for INR on warfarin alone. The error (confidence interval) associated with a prediction is ± 0.4 units. Similar linear relationships and prediction errors exist for Argatroban at a dose of 1 mcg/kg/min. Thus, for Argatroban doses of 1 or 2 mcg/kg/min, INR_W can be predicted from INR_{WA}. For Argatroban doses greater than 2 mcg/kg/min, the error associated with predicting INR_W from INR_{WA} is ±1. Thus, INR_W cannot be reliably predicted from INR_{WA} at doses greater than 2 mcg/kg/min.

SPECIAL POPULATIONS

Renal Impairment: No dosage adjustment is necessary in patients with renal dysfunction. The effect of renal disease on the pharmacokinetics of Argatroban was studied in 6 subjects with normal renal function (mean Clcr = 95 ± 16 mL/min) and in 18 subjects with mild (mean Clcr = 64 ± 10 mL/min), moderate (mean Clcr = 41 ± 5.8 mL/min), and severe (mean Clcr = 5 ± 7 mL/min) renal impairment. The pharmacokinetics and pharmacodynamics of Argatroban at dosages up to 5 mcg/kg/min were not significantly affected by renal dysfunction.

Hepatic Impairment: The dosage of Argatroban should be decreased in patients with hepatic impairment (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). Patients with hepatic impairment were not studied in percutaneous coronary intervention (PCI) trials. At a dose of 2.5 mcg/kg/min, hepatic impairment is associated with decreased clearance and increased elimination half-life of Argatroban (to 1.9 mL/kg/min and 181 minutes, respectively, for patients with a Child-Pugh score >6).

Age, Gender: There are no clinically significant effects of age or gender on the pharmacokinetics or pharmacodynamics (e.g., aPTT) of Argatroban.

Drug-Drug Interactions: ***Digoxin:*** In 12 healthy volunteers, intravenous infusion of Argatroban (2 mcg/kg/min) over 5 days (study days 11 to 15) did not affect the steady-state pharmacokinetics of oral digoxin (0.375 mg daily for 15 days).

Erythromycin: In 10 healthy subjects, orally administered erythromycin (a potent inhibitor of CYP3A4/5) at 500 mg four times daily for 7 days had no effect on the pharmacokinetics of Argatroban at a dose of 1 mcg/kg/min for 5 hours. These data suggest oxidative metabolism by CYP3A4/5 is not an important elimination pathway in vivo for Argatroban.

CLINICAL STUDIES

Heparin-Induced Thrombocytopenia: Heparin-induced thrombocytopenia (HIT) is a potentially serious, immune-mediated complication of heparin therapy that is strongly associated with subsequent venous and arterial thrombosis. Whereas initial treatment of HIT is to discontinue administration of all heparin, patients may require anticoagulation for prevention and treatment of thromboembolic events.

The conclusion that Argatroban is an effective treatment for heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia and thrombosis syndrome (HITTS) is based upon the data from an historically controlled efficacy and safety study (Study 1) and a follow-on efficacy and safety study (Study 2). These studies were comparable with regard to study design, study objectives, dosing regimens as well as study outline, conduct, and monitoring.

In these studies, 568 adult patients were treated with Argatroban and 193 adult patients made up the historical control group. Patients were required to have a clinical diagnosis of heparin-induced thrombocytopenia, either with-

Continued on next page

This product information is based on labeling in effect on August 1, 2003. Further information is available at: GlaxoSmithKline, PO Box 13398, Research Triangle Park, NC 27709. 1-888-825-5249. Corporate Web Site: www.gsk.com

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62% by loop and potassium-sparing diuretics and 102% by nonspecific beta-blockers. These effects on the metabolite are not expected to be of clinical consequence.

Effects of VIAGRA on Other Drugs

***In vitro* studies:** Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC50 >150 μM). Given sildenafil peak plasma concentrations of approximately 1 μM after recommended doses, it is unlikely that VIAGRA will alter the clearance of substrates of these isoenzymes.

***In vivo* studies:** When VIAGRA 100 mg oral was coadministered with amlodipine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.

No significant interactions were shown with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolized by CYP2C9.

VIAGRA (50 mg) did not potentiate the increase in bleeding time caused by aspirin (150 mg).

VIAGRA (50 mg) did not potentiate the hypotensive effect of alcohol in healthy volunteers with mean maximum blood alcohol levels of 0.08%.

In a study of healthy male volunteers, sildenafil (100 mg) did not affect the steady state pharmacokinetics of the HIV protease inhibitors, saquinavir and ritonavir, both of which are CYP3A4 substrates.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Sildenafil was not carcinogenic when administered to rats for 24 months at a dose resulting in total systemic drug exposure (AUCs) for unbound sildenafil and its major metabolite of 29- and 42-times, for male and female rats, respectively, the exposures observed in human males given the Maximum Recommended Human Dose (MRHD) of 100 mg.

Sildenafil was not carcinogenic when administered to mice for 18–21 months at dosages up to the Maximum Tolerated Dose (MTD) of 10 mg/kg/day, approximately 0.6 times the MRHD on a mg/m^2 basis.

Sildenafil was negative in *in vitro* bacterial and Chinese hamster ovary cell assays to detect mutagenicity, and *in vitro* human lymphocytes and *in vivo* mouse micronucleus assays to detect clastogenicity.

There was no impairment of fertility in rats given sildenafil up to 60 mg/kg/day for 36 days to females and 102 days to males, a dose producing an AUC value of more than 25 times the human male AUC.

There was no effect on sperm motility or morphology after single 100 mg oral doses of VIAGRA in healthy volunteers.

Pregnancy, Nursing Mothers and Pediatric Use

VIAGRA is not indicated for use in newborns, children, or women.

Pregnancy Category B. No evidence of teratogenicity, embryotoxicity or fetotoxicity was observed in rats and rabbits which received up to 200 mg/kg/day during organogenesis. These doses represent, respectively, about 20 and 40 times the MRHD on a mg/m^2 basis in a 50 kg subject. In the rat pre- and postnatal development study, the no observed adverse effect dose was 30 mg/kg/day given for 36 days. In the nonpregnant rat the AUC at this dose was about 20 times human AUC. There are no adequate and well-controlled studies of sildenafil in pregnant women.

Geriatric Use: Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil (see **CLINICAL PHARMACOLOGY: Pharmacokinetics in Special Populations**). Since higher plasma levels may increase both the efficacy and incidence of adverse events, a starting dose of 25 mg should be considered (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

PRE-MARKETING EXPERIENCE:

VIAGRA was administered to over 3700 patients (aged 19–87 years) during clinical trials worldwide. Over 550 patients were treated for longer than one year.

In placebo-controlled clinical studies, the discontinuation rate due to adverse events for VIAGRA (2.5%) was not significantly different from placebo (2.3%). The adverse events were generally transient and mild to moderate in nature.

In trials of all designs, adverse events reported by patients receiving VIAGRA were generally similar. In fixed-dose studies, the incidence of some adverse events increased with dose. The nature of the adverse events in flexible-dose studies, which more closely reflect the recommended dosage regimen, was similar to that for fixed-dose studies.

When VIAGRA was taken as recommended (on an as-needed basis) in flexible-dose, placebo-controlled clinical trials, the following adverse events were reported:

TABLE 2. ADVERSE EVENTS REPORTED BY ≥2% OF PATIENTS TREATED WITH VIAGRA AND MORE FREQUENT ON DRUG THAN PLACEBO IN PRN FLEXIBLE-DOSE PHASE II/III STUDIES

Adverse Event	Percentage of Patients Reporting Event	
	VIAGRA N = 734	PLACEBO N = 725
Headache	16%	4%
Flushing	10%	1%
Dyspepsia	7%	2%
Nasal Congestion	4%	2%
Urinary Tract Infection	3%	2%
Abnormal Vision†	3%	0%
Diarrhea	3%	1%
Dizziness	2%	1%
Rash	2%	1%

† Abnormal Vision: Mild and transient, predominantly color tinge to vision, but also increased sensitivity to light or blurred vision. In these studies, only one patient discontinued due to abnormal vision.

Other adverse reactions occurred at a rate of >2%, but equally common on placebo: respiratory tract infection, back pain, flu syndrome, and arthralgia.

In fixed-dose studies, dyspepsia (17%) and abnormal vision (11%) were more common at 100 mg than at lower doses. At doses above the recommended dose range, adverse events were similar to those detailed above but generally were reported more frequently.

The following events occurred in <2% of patients in controlled clinical trials; a causal relationship to VIAGRA is uncertain. Reported events include those with a plausible relation to drug use; omitted are minor events and reports too imprecise to be meaningful:

Body as a whole: face edema, photosensitivity reaction, shock, asthenia, pain, chills, accidental fall, abdominal pain, allergic reaction, chest pain, accidental injury.

Cardiovascular: angina pectoris, AV block, migraine, syncope, tachycardia, palpitation, hypotension, postural hypotension, myocardial ischemia, cerebral thrombosis, cardiac arrest, heart failure, abnormal electrocardiogram, cardiomyopathy.

Digestive: vomiting, glossitis, colitis, dysphagia, gastritis, gastroenteritis, esophagitis, stomatitis, dry mouth, liver function tests abnormal, rectal hemorrhage, gingivitis.

Hemic and Lymphatic: anemia and leukopenia.

Metabolic and Nutritional: thirst, edema, gout, unstable diabetes, hyperglycemia, peripheral edema, hyperuricemia, hypoglycemic reaction, hypernatremia.

Musculoskeletal: arthritis, arthrosis, myalgia, tendon rupture, tenosynovitis, bone pain, myasthenia, synovitis.

Nervous: ataxia, hypertonia, neuralgia, neuropathy, paresthesia, tremor, vertigo, depression, insomnia, somnolence, abnormal dreams, reflexes decreased, hypesthesia.

Respiratory: asthma, dyspnea, laryngitis, pharyngitis, sinusitis, bronchitis, sputum increased, cough increased.

Skin and Appendages: urticaria, herpes simplex, pruritus, sweating, skin ulcer, contact dermatitis, exfoliative dermatitis.

Special Senses: mydriasis, conjunctivitis, photophobia, tinnitus, eye pain, deafness, ear pain, eye hemorrhage, cataract, dry eyes.

Urogenital: cystitis, nocturia, urinary frequency, breast enlargement, urinary incontinence, abnormal ejaculation, genital edema and anorgasmia.

POST-MARKETING EXPERIENCE:

Cardiovascular and cerebrovascular

Serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, subarachnoid and intracerebral hemorrhages, and pulmonary hemorrhage have been reported post-marketing in temporal association with the use of VIAGRA. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of VIAGRA without sexual activity. Others were reported to have occurred hours to days after the use of VIAGRA and sexual activity. It is not possible to determine whether these events are related directly to VIAGRA, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors (see **WARNINGS** for further important cardiovascular information).

Other events

Other events reported post-marketing to have been observed in temporal association with VIAGRA and not listed in the pre-marketing adverse reactions section above include:

Nervous: seizure and anxiety.

Urogenital: prolonged erection, priapism (see **WARNINGS**) and hematuria.

Special Senses: diplopia, temporary vision loss/decreased vision, ocular redness or bloodshot appearance, ocular burning, ocular swelling/pressure, increased intraocular pressure, retinal vascular disease or bleeding, vitreous detachment/traction, paramacular edema and epistaxis.

OVERDOSAGE

In studies with healthy volunteers of single doses up to 800 mg, adverse events were similar to those seen at lower doses but incidence rates were increased.

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and it is not eliminated in the urine.

	25 mg	50 mg	100 mg
Obverse	VGR25	VGR50	VGR100
Reverse	PFIZER	PFIZER	PFIZER
Bottle of 30	NDC-0069-4200-30	NDC-0069-4210-30	NDC-0069-4220-30
Bottle of 100	N/A	NDC-0069-4210-66	NDC-0069-4220-66

DOSAGE AND ADMINISTRATION

For most patients, the recommended dose is 50 mg taken, as needed, approximately 1 hour before sexual activity. However, VIAGRA may be taken anywhere from 4 hours to 0.5 hour before sexual activity. Based on effectiveness and toleration, the dose may be increased to a maximum recommended dose of 100 mg or decreased to 25 mg. The maximum recommended dosing frequency is once per day.

The following factors are associated with increased plasma levels of sildenafil: age >65 (40% increase in AUC), hepatic impairment (e.g., cirrhosis, 80%), severe renal impairment (creatinine clearance <30 mL/min, 100%), and concomitant use of potent cytochrome P450 3A4 inhibitors [ketoconazole, itraconazole, erythromycin (182%), saquinavir (210%)]. Since higher plasma levels may increase both the efficacy and incidence of adverse events, a starting dose of 25 mg should be considered in these patients.

Ritonavir greatly increased the systemic level of sildenafil in a study of healthy, non-HIV infected volunteers (11-fold increase in AUC, see **Drug Interactions**.) Based on these pharmacokinetic data, it is recommended not to exceed a maximum single dose of 25 mg of VIAGRA in a 48 hour period.

VIAGRA was shown to potentiate the hypotensive effects of nitrates and its administration in patients who use nitric oxide donors or nitrates in any form is therefore contraindicated.

Simultaneous administration of VIAGRA doses above 25 mg and an alpha-blocker may lead to symptomatic hypotension in some patients. Doses of 50 mg or 100 mg of VIAGRA should not be taken within 4 hours of alpha-blocker administration. A 25 mg dose of VIAGRA may be taken at any time.

HOW SUPPLIED

VIAGRA® (sildenafil citrate) is supplied as blue, film-coated, rounded-diamond-shaped tablets containing sildenafil citrate equivalent to the nominally indicated amount of sildenafil as follows:

[See table above]

Recommended Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

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Pfizer Labs

Division of Pfizer Inc, NY, NY 10017

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Shown in Product Identification Guide, page 332

VIBRAMYCIN® ℞

[*vī-bră-mī-sĭn*]

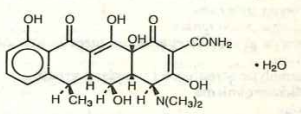
Calcium
(doxycycline calcium)
oral suspension
SYRUP
Hyclate
(doxycycline hyclate)
CAPSULES
Monohydrate
(doxycycline monohydrate)
for ORAL SUSPENSION

VIBRA-TABS®
(doxycycline hyclate)
FILM COATED TABLETS

DESCRIPTION

Vibramycin® is a broad-spectrum antibiotic synthetically derived from oxytetracycline, and is available as Vibramycin Monohydrate (doxycycline monohydrate); Vibramycin Hyclate and Vibra-Tabs (doxycycline hydrochloride hemiethanolate hemihydrate); and Vibramycin Calcium (doxycycline calcium) for oral administration.

The structural formula of doxycycline monohydrate is



with a molecular formula of $C_{22}H_{24}N_2O_8 \cdot H_2O$ and a molecular weight of 462.46. The chemical designation for doxycycline is 4-(Dimethylamino)-1, 4, 4a, 5, 5a, 6, 11, 12a-octahydro-3, 5, 10, 12, 12a-pentahydroxy-6-methyl-1, 11-dioxo-2-naphthacenecarboxamide monohydrate. The molecular formula for doxycycline hydrochloride hemiethanolate hemihydrate is $(C_{22}H_{24}N_2O_8 \cdot HCl)_2 \cdot C_2H_6O \cdot H_2O$ and the

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Vibramycin—Cont.

molecular weight is 1025.89. Doxycycline is a light-yellow crystalline powder. Doxycycline hyclate is soluble in water, while doxycycline monohydrate is very slightly soluble in water.

Doxycycline has a high degree of lipoid solubility and a low affinity for calcium binding. It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form.

Inert ingredients in the syrup formulation are: apple flavor; butylparaben; calcium chloride; carmine; glycerin; hydrochloric acid; magnesium aluminum silicate; povidone; propylene glycol; propylparaben; raspberry flavor; simethicone emulsion; sodium hydroxide; sodium metabisulfite; sorbitol solution; water.

Inert ingredients in the capsule formulations are: hard gelatin capsules (which may contain Blue 1 and other inert ingredients); magnesium stearate; microcrystalline cellulose; sodium lauryl sulfate.

Inert ingredients for the oral suspension formulation are: carboxymethylcellulose sodium; Blue 1; methylparaben; microcrystalline cellulose; propylparaben; raspberry flavor; Red 28; simethicone emulsion; sucrose.

Inert ingredients for the tablet formulation are: ethylcellulose; hydroxypropyl methylcellulose; magnesium stearate; microcrystalline cellulose; propylene glycol; sodium lauryl sulfate; talc; titanium dioxide; Yellow 6 Lake.

CLINICAL PHARMACOLOGY

Tetracyclines are readily absorbed and are bound to plasma proteins in varying degree. They are concentrated by the liver in the bile, and excreted in the urine and feces at high concentrations and in a biologically active form. Doxycycline is virtually completely absorbed after oral adminstration.

Following a 200 mg dose, normal adult volunteers averaged peak serum levels of 2.6 mcg/mL of doxycycline at 2 hours decreasing to 1.45 mcg/mL at 24 hours. Excretion of doxycycline by the kidney is about 40%/72 hours in individuals with normal function (creatinine clearance about 75 mL/min.). This percentage excretion may fall as low as 1-5%/72 hours in individuals with severe renal insufficiency (creatinine clearance below 10 mL/min.). Studies have shown no significant difference in serum half-life of doxycycline (range 18-22 hours) in individuals with normal and severely impaired renal function.

Hemodialysis does not alter serum half-life.

Results of animal studies indicate that tetracyclines cross the placenta and are found in fetal tissues.

Microbiology

The tetracyclines are primarily bacteriostatic and are thought to exert their antimicrobial effect by the inhibition of protein synthesis. The tetracyclines, including doxycycline, have a similar antimicrobial spectrum of activity against a wide range of gram-positive and gram-negative organisms. Cross-resistance of these organisms to tetracyclines is common.

Gram-Negative Bacteria

Neisseria gonorrhoeae
Calymmatobacterium granulomatis
Haemophilus ducreyi
Haemophilus influenzae
Yersinia pestis (formerly *Pasteurella pestis*)
Francisella tularensis (formerly *Pasteurella tularensis*)
Vibrio cholerae (formerly *Vibrio comma*)
Bartonella bacilliformis
Brucella species

Because many strains of the following groups of gram-negative microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are recommended:

Escherichia coli
Klebsiella species
Enterobacter aerogenes
Shigella species
Acinetobacter species (formerly *Mima* species and *Herellea* species)
Bacteroides species

Gram-Positive Bacteria

Because many strains of the following groups of gram-positive microorganisms have been shown to be resistant to tetracycline, culture and susceptibility testing are recommended. Up to 44 percent of strains of *Streptococcus pyogenes* and 74 percent of *Streptococcus faecalis* have been found to be resistant to tetracycline drugs. Therefore, tetracycline should not be used for streptococcal disease unless the organism has been demonstrated to be susceptible.

Streptococcus pyogenes
Streptococcus pneumoniae
Enterococcus group (*Streptococcus faecalis* and *Streptococcus faecium*)
Alpha-hemolytic streptococci (viridans group)

Other Microorganisms

Rickettsiae
Chlamydia psittaci
Chlamydia trachomatis
Mycoplasma pneumoniae
Ureaplasma urealyticum
Borrelia recurrentis
Treponema pallidum
Treponema pertenue
Clostridium species
Fusobacterium fusiforme
Actinomyces species
Bacillus anthracis
Propionibacterium acnes
Entamoeba species
Balantidium coli
Plasmodium falciparum

Doxycycline has been found to be active against the asexual erythrocytic forms of *Plasmodium falciparum* but not against the gametocytes of *P. falciparum*. The precise mechanism of action of the drug is not known.

Susceptibility tests: Diffusion techniques: Quantitative methods that require measurement of zone diameters give the most precise estimate of the susceptibility of bacteria to antimicrobial agents. One such standard procedure[1] which has been recommended for use with disks to test susceptibility of organisms to doxycycline uses the 30-mcg tetracycline-class disk or the 30-mcg doxycycline disk. Interpretation involves the correlation of the diameter obtained in the disk test with the minimum inhibitory concentration (MIC) for tetracycline or doxycycline, respectively.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 30-mcg tetracycline-class disk or the 30-mcg doxycycline disk should be interpreted according to the following criteria:

Zone Diameter (mm)		Interpretation
tetracycline	doxycycline	
≥19	≥16	Susceptible
15-18	13-15	Intermediate
≤14	≤12	Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Intermediate" suggests that the organism would be susceptible if a high dosage is used or if the infection is confined to tissues and fluids in which high antimicrobial levels are attained. A report of "Resistant" indicates that achievable concentrations are unlikely to be inhibitory, and other therapy should be selected.

Standardized procedures require the use of laboratory control organisms. The 30-mcg tetracycline-class disk or the 30-mcg doxycycline disk should give the following zone diameters:

Organism	Zone Diameter (mm)	
	tetracycline	doxycycline
E. coli ATCC 25922	18-25	18-24
S. aureus ATCC 25923	19-28	23-29

Dilution techniques: Use a standardized dilution method[2] (broth, agar, microdilution) or equivalent with tetracycline powder. The MIC values obtained should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤4	Susceptible
8	Intermediate
≥16	Resistant

As with standard diffusion techniques, dilution methods require the use of laboratory control organisms. Standard tetracycline powder should provide the following MIC values:

Organism	MIC (mcg/mL)
E. coli ATCC 25922	1.0-4.0
S. aureus ATCC 29213	0.25-1.0
E. faecalis ATCC 29212	8-32
P. aeruginosa ATCC 27853	8-32

INDICATIONS AND USAGE

Treatment:

Doxycycline is indicated for the treatment of the following infections:

- Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox, and tick fevers caused by Rickettsiae.
- Respiratory tract infections caused by *Mycoplasma pneumoniae*.
- Lymphogranuloma venereum caused by *Chlamydia trachomatis*.
- Psittacosis (ornithosis) caused by *Chlamydia psittaci*.
- Trachoma caused by *Chlamydia trachomatis*, although the infectious agent is not always eliminated as judged by immunofluorescence.
- Inclusion conjunctivitis caused by *Chlamydia trachomatis*.
- Uncomplicated urethral, endocervical or rectal infections in adults caused by *Chlamydia trachomatis*.
- Nongonococcal urethritis caused by *Ureaplasma urealyticum*.
- Relapsing fever due to *Borrelia recurrentis*.

Doxycycline is also indicated for the treatment of infections caused by the following gram-negative microorganisms:

- Chancroid caused by *Haemophilus ducreyi*.
- Plague due to *Yersinia pestis* (formerly *Pasteurella pestis*).
- Tularemia due to *Francisella tularensis* (formerly *Pasteurella tularensis*).
- Cholera caused by *Vibrio cholerae* (formerly *Vibrio comma*).
- Campylobacter fetus infections caused by *Campylobacter fetus* (formerly *Vibrio fetus*).
- Brucellosis due to *Brucella* species (in conjunction with streptomycin).
- Bartonellosis due to *Bartonella bacilliformis*.
- Granuloma inguinale caused by *Calymmatobacterium granulomatis*.

Because many strains of the following groups of microorganisms have been shown to be resistant to doxycycline, culture and susceptibility testing are recommended.

Doxycycline is indicated for treatment of infections caused by the following gram-negative microorganisms, when bacteriologic testing indicates appropriate susceptibility to the drug:

- *Escherichia coli*.
- *Enterobacter aerogenes* (formerly *Aerobacter aerogenes*).
- *Shigella* species.
- *Acinetobacter* species (formerly *Mima* species and *Herellea* species).
- Respiratory tract infections caused by *Haemophilus influenzae*.
- Respiratory tract and urinary tract infections caused by *Klebsiella* species.

Doxycycline is indicated for treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:

- Upper respiratory infections caused by *Streptococcus pneumoniae* (formerly *Diplococcus pneumoniae*).

Anthrax due to *Bacillus anthracis*, including inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*.

When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of the following infections:

- Uncomplicated gonorrhea caused by *Neisseria gonorrhoeae*.
- Syphilis caused by *Treponema pallidum*.
- Yaws caused by *Treponema pertenue*.
- Listeriosis due to *Listeria monocytogenes*.
- Vincent's infection caused by *Fusobacterium fusiforme*.
- Actinomycosis caused by *Actinomyces israelii*.
- Infections caused by *Clostridium* species.

In acute intestinal amebiasis, doxycycline may be a useful adjunct to amebicides.

In severe acne, doxycycline may be useful adjunctive therapy.

Prophylaxis:

Doxycycline is indicated for the prophylaxis of malaria due to *Plasmodium falciparum* in short-term travelers (<4 months) to areas with chloroquine and/or pyrimethamine-sulfadoxine resistant strains. See DOSAGE AND ADMINISTRATION section and Information for Patients subsection of the PRECAUTIONS section.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

WARNINGS

THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY AND CHILDHOOD TO THE AGE OF 8 YEARS) MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH (YELLOW-GRAY-BROWN). This adverse reaction is more common during long-term use of the drugs, but it has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED IN THIS AGE GROUP, EXCEPT FOR ANTHRAX, INCLUDING INHALATIONAL ANTHRAX (POST-EXPOSURE), UNLESS OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including doxycycline, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy. If any tetracycline is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

The antianabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ul-

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traviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema.

Vibramycin Syrup contains sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

PRECAUTIONS

General

As with other antibiotic preparations, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy instituted.

Bulging fontanels in infants and benign intracranial hypertension in adults have been reported in individuals receiving tetracyclines. These conditions disappeared when the drug was discontinued.

Incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy, when indicated.

Doxycycline offers substantial but not complete suppression of the asexual blood stages of *Plasmodium* strains.

Doxycycline does not suppress *P. falciparum's* sexual blood stage gametocytes. Subjects completing this prophylactic regimen may still transmit the infection to mosquitoes outside endemic areas.

Information for Patients

Patients taking doxycycline for malaria prophylaxis should be advised:

- that no present-day antimalarial agent, including doxycycline, guarantees protection against malaria.
- to avoid being bitten by mosquitoes by using personal protective measures that help avoid contact with mosquitoes, especially from dusk to dawn (e.g., staying in well-screened areas, using mosquito nets, covering the body with clothing, and using an effective insect repellent).
- that doxycycline prophylaxis:
  - should begin 1-2 days before travel to the malarious area,
  - should be continued daily while in the malarious area and after leaving the malarious area,
  - should be continued for 4 further weeks to avoid development of malaria after returning from an endemic area,
  - should not exceed 4 months.

All patients taking doxycycline should be advised:

- to avoid excessive sunlight or artificial ultraviolet light while receiving doxycycline and to discontinue therapy if phototoxicity (e.g., skin eruption, etc.) occurs. Sunscreen or sunblock should be considered (See WARNINGS.)
- to drink fluids liberally along with doxycycline to reduce the risk of esophageal irritation and ulceration. (See ADVERSE REACTIONS.)
- that the absorption of tetracyclines is reduced when taken with foods, especially those which contain calcium. However, the absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk. (See DRUG INTERACTIONS.)
- that the absorption of tetracyclines is reduced when taking bismuth subsalicylate (See DRUG INTERACTIONS.)
- that the use of doxycycline might increase the incidence of vaginal candidiasis.

Laboratory Tests

In venereal disease, when co-existent syphilis is suspected, dark field examinations should be done before treatment is started and the blood serology repeated monthly for at least 4 months.

In long-term therapy, periodic laboratory evaluation of organ systems, including hematopoietic, renal, and hepatic studies, should be performed.

Drug Interactions

Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracyclines in conjunction with penicillin.

Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, or magnesium, and iron-containing preparations.

Absorption of tetracyclines is impaired by bismuth subsalicylate.

Barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline.

The concurrent use of tetracycline and Penthrane® (methoxyflurane) has been reported to result in fatal renal toxicity.

Concurrent use of tetracycline may render oral contraceptives less effective.

Drug/Laboratory Test Interactions

False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential of doxycycline have not been conducted. However, there has been evidence of oncogenic activity in rats in studies with the related antibiotics, oxytetracycline (adrenal and pituitary tumors), and minocycline (thyroid tumors).

Likewise, although mutagenicity studies of doxycycline have not been conducted, positive results in *in vitro* mammalian cell assays have been reported for related antibiotics (tetracycline, oxytetracycline).

Doxycycline administered orally at dosage levels as high as 250 mg/kg/day had no apparent effect on the fertility of female rats. Effect on male fertility has not been studied.

Pregnancy: Teratogenic Effects. Pregnancy Category D: There are no adequate and well-controlled studies on the use of doxycycline in pregnant women. The vast majority of reported experience with doxycycline during human pregnancy is short-term, first trimester exposure. There are no human data available to assess the effects of long-term therapy of doxycycline in pregnant women such as that proposed for treatment of anthrax exposure. An expert review of published data on experiences with doxycycline use during pregnancy by TERIS – the Teratogen Information System – concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as limited to fair), but the data are insufficient to state that there is no risk[a]. A case-control study (18,515 mothers of infants with congenital anomalies and 32,804 mothers of infants with no congenital anomalies) shows a weak but marginally statistically significant association with total malformations and use of doxycycline anytime during pregnancy. Sixty-three (0.19%) of the controls and fifty-six (0.30%) of the cases were treated with doxycycline. This association was not seen when the analysis was confined to maternal treatment during the period of organogenesis (i.e., in the second and third months of gestation) with the exception of a marginal relationship with neural tube defect based on only two exposed cases[b].

A small prospective study of 81 pregnancies describes 43 pregnant women treated for 10 days with doxycycline during early first trimester. All mothers reported their exposed infants were normal at 1 year of age[c].

Nonteratogenic effects: (See WARNINGS).

Labor and Delivery

The effect of tetracyclines on labor and delivery is unknown.

Nursing Mothers

Tetracyclines are excreted in human milk; however, the extent of absorption of tetracyclines, including doxycycline, by the breastfed infant is not known. Short-term use by lactating women is not necessarily contraindicated; however, the effects of prolonged exposure to doxycycline in breast milk are unknown[d]. Because of the potential for serious adverse reactions in nursing infants from doxycycline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. (See WARNINGS.)

Pediatric Use

See WARNINGS and DOSAGE AND ADMINISTRATION.

ADVERSE REACTIONS

Due to oral doxycycline's virtually complete absorption, side effects of the lower bowel, particularly diarrhea, have been infrequent. The following adverse reactions have been observed in patients receiving tetracyclines:

Gastrointestinal: anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region. Hepatotoxicity has been reported rarely. These reactions have been caused by both the oral and parenteral administration of tetracyclines. Rare instances of esophagitis and esophageal ulcerations have been reported in patients receiving capsule and tablet forms of the drugs in the tetracycline class. Most of these patients took medications immediately before going to bed. (See DOSAGE AND ADMINISTRATION.)

Skin: maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above. (See WARNINGS.)

Renal toxicity: Rise in BUN has been reported and is apparently dose related. (See WARNINGS.)

Hypersensitivity reactions: urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, serum sickness, pericarditis, and exacerbation of systemic lupus erythematosus.

Blood: Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported.

Other: bulging fontanels in infants and intracranial hypertension in adults. (See PRECAUTIONS – General.)

When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of the thyroid gland. No abnormalities of thyroid function studies are known to occur.

OVERDOSAGE

In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures. Dialysis does not alter serum half-life and thus would not be of benefit in treating cases of overdosage.

DOSAGE AND ADMINISTRATION

THE USUAL DOSAGE AND FREQUENCY OF ADMINISTRATION OF DOXYCYCLINE DIFFERS FROM THAT OF THE OTHER TETRACYCLINES. EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS. Adults: The usual dose of oral doxycycline is 200 mg on the first day of treatment (administered 100 mg every 12 hours) followed by a maintenance dose of 100 mg/day. The maintenance dose may be administered as a single dose or as 50 mg every 12 hours.

In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended.

For children above eight years of age: The recommended dosage schedule for children weighing 100 pounds or less is 2 mg/lb of body weight divided into two doses on the first day of treatment, followed by 1 mg/lb of body weight given as a single daily dose or divided into two doses, on subsequent days. For more severe infections up to 2 mg/lb of body weight may be used. For children over 100 lb the usual adult dose should be used.

The therapeutic antibacterial serum activity will usually persist for 24 hours following recommended dosage.

When used in streptococcal infections, therapy should be continued for 10 days.

Administration of adequate amounts of fluid along with capsule and tablet forms of drugs in the tetracycline class is recommended to wash down the drugs and reduce the risk of esophageal irritation and ulceration. (See ADVERSE REACTIONS.)

If gastric irritation occurs, it is recommended that doxycycline be given with food or milk. The absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk.

Studies to date have indicated that administration of doxycycline at the usual recommended doses does not lead to excessive accumulation of the antibiotic in patients with renal impairment.

Uncomplicated gonococcal infections in adults (except anorectal infections in men): 100 mg, by mouth, twice a day for 7 days. As an alternate single visit dose, administer 300 mg stat followed in one hour by a second 300 mg dose. The dose may be administered with food, including milk or carbonated beverage, as required.

Uncomplicated urethral, endocervical, or rectal infection in adults caused by *Chlamydia trachomatis:* 100 mg by mouth twice a day for 7 days.

Nongonococcal urethritis (NGU) caused by *C. trachomatis* or *U. urealyticum:* 100 mg by mouth twice a day for 7 days.

Syphilis – early: Patients who are allergic to penicillin should be treated with doxycycline 100 mg by mouth twice a day for 2 weeks.

Syphilis of more than one year's duration: Patients who are allergic to penicillin should be treated with doxycycline 100 mg by mouth twice a day for 4 weeks.

Acute epididymo-orchitis caused by *N. gonorrhoeae:* 100 mg, by mouth, twice a day for at least 10 days.

Acute epididymo-orchitis caused by *C. trachomatis:* 100 mg, by mouth, twice a day for at least 10 days.

For prophylaxis of malaria: For adults, the recommended dose is 100 mg daily. For children over 8 years of age, the recommended dose is 2 mg/kg given once daily up to the adult dose. Prophylaxis should begin 1-2 days before travel to the malarious area. Prophylaxis should be continued daily during travel in the malarious area and for 4 weeks after the traveler leaves the malarious area.

Inhalational anthrax (post-exposure):

ADULTS: 100 mg of doxycycline, by mouth, twice a day for 60 days.

CHILDREN: weighing less than 100 lb (45 kg); 1 mg/lb (2.2 mg/kg) of body weight, by mouth, twice a day for 60 days. Children weighing 100 lb or more should receive the adult dose.

HOW SUPPLIED

Vibramycin® Hyclate (doxycycline hyclate) is available in capsules containing doxycycline hyclate equivalent to:

50 mg doxycycline
bottles of 50 (NDC 0069-0940-50)

The capsules are white and light blue and are imprinted with "VIBRA" on one half and "PFIZER 094" on the other half.

100 mg doxycycline
bottles of 50 (NDC 0069-0950-50)

The capsules are light blue and are imprinted with "VIBRA" on one half and "PFIZER 095" on the other half.

Vibra-Tabs® (doxycycline hyclate) is available in salmon colored film-coated tablets containing doxycycline hyclate equivalent to:

100 mg doxycycline
bottles of 50 (NDC 0069-0990-50)

The tablets are imprinted on one side with "VIBRA-TABS" and "PFIZER 099" on the other side.

Vibramycin® Calcium Syrup (doxycycline calcium) oral suspension is available as a raspberry-apple flavored oral suspension. Each teaspoonful (5 mL) contains doxycycline calcium equivalent to 50 mg of doxycycline: 1 pint (473 mL) bottles (NDC 0069-0971-93).

Vibramycin® Monohydrate (doxycycline monohydrate) for Oral Suspension is available as a raspberry-flavored, dry powder for oral suspension. When reconstituted, each teaspoonful (5 mL) contains doxycycline monohydrate equivalent to 25 mg of doxycycline: 2 oz (60 mL) bottles (NDC 0069-0970-65).

All products are to be stored below 86°F (30°C) and dispensed in tight, light-resistant containers (USP).

ANIMAL PHARMACOLOGY AND ANIMAL TOXICOLOGY

Hyperpigmentation of the thyroid has been produced by members of the tetracycline class in the following species: in rats by oxytetracycline, doxycycline, tetracycline PO_4, and

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methacycline; in minipigs by doxycycline, minocycline, tetracycline PO_4, and methacycline; in dogs by doxycycline and minocycline; in monkeys by minocycline.
Minocycline, tetracycline PO_4, methacycline, doxycycline, tetracycline base, oxytetracycline HCl, and tetracycline HCl were goitrogenic in rats fed a low iodine diet. This goitrogenic effect was accompanied by high radioactive iodine uptake. Administration of minocycline also produced a large goiter with high radioiodine uptake in rats fed a relatively high iodine diet.
Treatment of various animal species with this class of drugs has also resulted in the induction of thyroid hyperplasia in the following: in rats and dogs (minocycline); in chickens (chlortetracycline); and in rats and mice (oxytetracycline). Adrenal gland hyperplasia has been observed in goats and rats treated with oxytetracycline.

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VIBRAMYCIN® Hyclate ℞

[vī "bra-mī 'sin]
doxycycline hyclate for injection
INTRAVENOUS
FOR INTRAVENOUS USE ONLY

DESCRIPTION

Vibramycin (doxycycline hyclate for injection) Intravenous is a broad-spectrum antibiotic synthetically derived from oxytetracycline, and is available as Vibramycin Hyclate (doxycycline hydrochloride hemiethanolate hemihydrate). The chemical designation of this light-yellow crystalline powder is alpha-6-deoxy-5-oxytetracycline. Doxycycline has a high degree of lipoid solubility and a low affinity for calcium binding. It is highly stable in normal human serum.

ACTIONS

Doxycycline is primarily bacteriostatic and thought to exert its antimicrobial effect by the inhibition of protein synthesis. Doxycycline is active against a wide range of gram-positive and gram-negative organisms.
The drugs in the tetracycline class have closely similar antimicrobial spectra and cross resistance among them is common. Microorganisms may be considered susceptible to doxycycline (likely to respond to doxycycline therapy) if the minimum inhibitory concentration (M.I.C.) is not more than 4.0 mcg/mL. Microorganisms may be considered intermediate (harboring partial resistance) if the M.I.C. is 4.0 to 12.5 mcg/mL and resistant (not likely to respond to therapy) if the M.I.C. is greater than 12.5 mcg/mL.
Susceptibility plate testing: If the Kirby-Bauer method of disc susceptibility testing is used, a 30 mcg doxycycline disc should give a zone of at least 16 mm when tested against a doxycycline-susceptible bacterial strain. A tetracycline disc may be used to determine microbial susceptibility. If the Kirby-Bauer method of disc susceptibility testing is used, a 30 mcg tetracycline disc should give a zone of at least 19 mm when tested against a tetracycline-susceptible bacterial strain.
Tetracyclines are readily absorbed and are bound to plasma proteins in varying degree. They are concentrated by the liver in the bile, and excreted in the urine and feces at high concentrations and in a biologically active form.
Following a single 100 mg dose administered in a concentration of 0.4 mg/mL in a one-hour infusion, normal adult volunteers average a peak of 2.5 mcg/mL, while 200 mg of a concentration of 0.4 mg/mL administered over two hours averaged a peak of 3.6 mcg/mL. Excretion of doxycycline by the kidney is about 40 percent/72 hours in individuals with normal function (creatinine clearance about 75 mL/min.). This percentage excretion may fall as low as 1–5 percent/72 hours in individuals with severe renal insufficiency (creatinine clearance below 10 mL/min.). Studies have shown no significant difference in serum half-life of doxycycline (range 18–22 hours) in individuals with normal and severely impaired renal function.
Hemodialysis does not alter this serum half-life of doxycycline.

INDICATIONS

Doxycycline is indicated in infections caused by the following microorganisms:
Rickettsiae (Rocky Mountain spotted fever, typhus fever, and the typhus group, Q fever, rickettsialpox and tick fevers).
Mycoplasma pneumoniae (PPLO, Eaton Agent).
Agents of psittacosis and ornithosis.
Agents of lymphogranuloma venereum and granuloma inguinale.
The spirochetal agent of relapsing fever (*Borrelia recurrentis*).
The following gram-negative microorganisms:
Haemophilus ducreyi (chancroid),
Pasteurella pestis and *Pasteurella tularensis*,
Bartonella bacilliformis,
Bacteroides species,
Vibrio comma and *Vibrio fetus*,
Brucella species (in conjunction with streptomycin).
Because many strains of the following groups of microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are recommended.
Doxycycline is indicated for treatment of infections caused by the following gram-negative microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:
Escherichia coli,
Enterobacter aerogenes (formerly *Aerobacter aerogenes*),
Shigella species,
Mima species and *Herellea* species,
Haemophilus influenzae (respiratory infections),
Klebsiella species (respiratory and urinary infections).
Doxycycline is indicated for treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:
Streptococcus species:
Up to 44 percent of strains of *Streptococcus pyogenes* and 74 percent of *Streptococcus faecalis* have been found to be resistant to tetracycline drugs. Therefore, tetracyclines should not be used for streptococcal disease unless the organism has been demonstrated to be sensitive.
For upper respiratory infections due to group A beta-hemolytic streptococci, penicillin is the usual drug of choice, including prophylaxis of rheumatic fever.
Diplococcus pneumoniae,
Staphylococcus aureus, respiratory skin and soft tissue infections. Tetracyclines are not the drugs of choice in the treatment of any type of staphylococcal infections.
Anthrax due to *Bacillus anthracis*, including inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*.
When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of infections due to:
Neisseria gonorrhoeae and *N. meningitidis*,
Treponema pallidum and *Treponema pertenue* (syphilis and yaws),
Listeria monocytogenes,
Clostridium species,
Fusobacterium fusiforme (Vincent's infection),
Actinomyces species.
In acute intestinal amebiasis, doxycycline may be a useful adjunct to amebicides.
Doxycycline is indicated in the treatment of trachoma, although the infectious agent is not always eliminated, as judged by immunofluorescence.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

WARNINGS

THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY AND CHILDHOOD TO THE AGE OF 8 YEARS) MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH (YELLOW-GRAY-BROWN). This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported.
TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED IN THIS AGE GROUP, EXCEPT FOR ANTHRAX, INCLUDING INHALATIONAL ANTHRAX (POST-EXPOSURE), UNLESS OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED.
Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light, should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema. The antianabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.

Usage in Pregnancy

(See above WARNINGS about use during tooth development.)
Vibramycin Intravenous has not been studied in pregnant patients. It should not be used in pregnant women unless, in the judgment of the physician, it is essential for the welfare of the patient.
Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy.

Usage in Children

The use of Vibramycin Intravenous in children under 8 years is not recommended because safe conditions for its use have not been established.
(See above WARNINGS about use during tooth development.)
As with other tetracyclines, doxycycline forms a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued.
Tetracyclines are present in the milk of lactating women who are taking a drug in this class.

PRECAUTIONS

As with other antibiotic preparations, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy instituted.
In venereal diseases when coexistent syphilis is suspected, a dark field examination should be done before treatment is started and the blood serology repeated monthly for at least 4 months.
Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.
In long-term therapy, periodic laboratory evaluation of organ systems, including hematopoietic, renal, and hepatic studies should be performed. All infections due to group A beta-hemolytic streptococci should be treated for at least 10 days.
Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline in conjunction with penicillin.

ADVERSE REACTIONS

Gastrointestinal: anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region. Hepatotoxicity has been reported rarely. These reactions have been caused by both the oral and parenteral administration of tetracyclines.
Skin: maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above. (See WARNINGS.)
Renal toxicity: Rise in BUN has been reported and is apparently dose related. (See WARNINGS.)
Hypersensitivity reactions: urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis and exacerbation of systemic lupus erythematosus.
Bulging fontanels in infants and benign intracranial hypertension in adults have been reported in individuals receiving full therapeutic dosages. These conditions disappeared rapidly when the drug was discontinued.
Blood: Hemolytic anemia, thrombocytopenia, neutropenia and eosinophilia have been reported.
When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function studies are known to occur.

DOSAGE AND ADMINISTRATION

Note: Rapid administration is to be avoided. Parenteral therapy is indicated only when oral therapy is not indicated. Oral therapy should be instituted as soon as possible. If intravenous therapy is given over prolonged periods of time, thrombophlebitis may result.
THE USUAL DOSAGE AND FREQUENCY OF ADMINISTRATION OF VIBRAMYCIN I.V. (100-200 MG/DAY) DIFFERS FROM THAT OF THE OTHER TETRACYCLINES (1-2 G/DAY). EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS.
Studies to date have indicated that Vibramycin at the usual recommended doses does not lead to excessive accumulation of the antibiotic in patients with renal impairment.
Adults: The usual dosage of Vibramycin I.V. is 200 mg on the first day of treatment administered in one or two infusions. Subsequent daily dosage is 100 to 200 mg depending upon the severity of infection, with 200 mg administered in one or two infusions.
In the treatment of primary and secondary syphilis, the recommended dosage is 300 mg daily for at least 10 days.
In the treatment of inhalational anthrax (post-exposure) the recommended dose is 100 mg of doxycycline, twice a day.
Parenteral therapy is only indicated when oral therapy is not indicated and should not be continued over a prolonged period of time. Oral therapy should be instituted as soon as possible. Therapy must continue for a total of 60 days.
For children above eight years of age: The recommended dosage schedule for children weighing 100 pounds or less is 2 mg/lb of body weight on the first day of treatment, administered in one or two infusions. Subsequent daily dosage is 1 to 2 mg/lb of body weight given as one or two infusions,

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