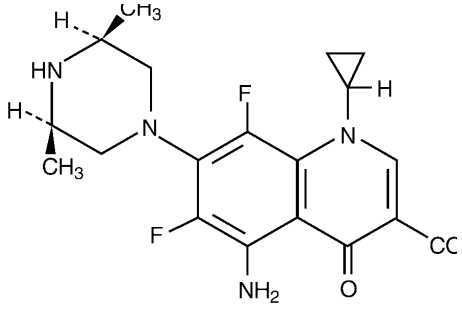
once-a-day
ZAgAm®
sparfloxacin
200 mg TABLETS™

Rx only

DESCRIPTION: Zagam® (sparfloxacin) tablets contain sparfloxacin, a synthetic broad-spectrum antimicrobial agent for oral administration. Sparfloxacin, an aminodifluoroquinolone, is 5-Amino-1-cyclopropyl-7-(*cis*-3,5-dimethyl-1-piperazinyl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid. Its empirical formula is $C_{19}H_{22}F_2N_4O_3$ and it has the following chemical structure:



Sparfloxacin has a molecular weight of 392.41. It occurs as a yellow crystalline powder. It is sparingly soluble in glacial acetic acid or chloroform, very slightly soluble in ethanol (95%), and practically insoluble in water and ether. It dissolves in dilute acetic acid or 0.1 N sodium hydroxide.

Zagam is available as a 200-mg round, white film-coated tablet. Each 200-mg tablet contains the following inactive ingredients: microcrystalline cellulose NF, corn

starch NF, L-hydroxypropylcellulose NF, magnesium stearate NF, and colloidal silicone dioxide NF. The film coating contains: methylhydroxypropylcellulose USP, polyethylene glycol 6000, and titanium dioxide USP.

CLINICAL PHARMACOLOGY: Absorption: Sparfloxacin is well absorbed following oral administration with an absolute oral bioavailability of 92%. The mean maximum plasma sparfloxacin concentration following a single 400-mg oral dose was approximately 1.3 (±0.2) μg/mL. The area under the curve (mean $AUC_{0\rightarrow\infty}$) following a single 400-mg oral dose was approximately 34 (±6.8) μg•hr/mL.

Steady-state plasma concentration was achieved on the first day by giving a loading dose that was double the daily dose. Mean (± SD) pharmacokinetic parameters observed for the 24-hour dosing interval with the recommended dosing regimen are shown below:

Dosing Regimen (mg/day)	**Peak Cmax (μg/mL)**	**Trough C_{24} (μg/mL)**	**$AUC_{0\rightarrow24}$ hr. μg/mL**
400 mg loading dose (day 1)	1.3 (±0.2)	0.5 (±0.1)	20.6 (±3.1)
200 mg q24 hours (steady-state)	1.1 (±0.1)	0.5 (±0.1)	18.7 (±2.6)

Maximum plasma concentrations for the initial oral 400-mg loading dose were typically achieved between 3 to 6 hours following administration with a mean value of approximately 4 hours. Maximum plasma concentrations for a 200-mg dose were also achieved between 3 to 6 hours after administration with a mean of about 4 hours.

Oral absorption of sparfloxacin is unaffected by administration with milk or food, including high fat meals. Concurrent administration of antacids containing magnesium hydroxide and aluminum hydroxide reduces the oral bioavailability of sparfloxacin by as much as 50%. (See **PRECAUTIONS: Information for Patients** and **Drug Interactions**.)

Distribution: Upon reaching general circulation, sparfloxacin distributes well into the body, as reflected by the large mean steady-state volume of distribution (Vd_{ss}) of 3.9 (±0.8) L/kg. Sparfloxacin exhibits low plasma protein binding in serum at about 45%.

Sparfloxacin penetrates well into body fluids and tissues. Results of tissue and body fluid distribution studies demonstrated that oral administration of sparfloxacin produces sustained concentrations and that sparfloxacin concentrations in lower respiratory tract tissues and fluids generally exceed the corresponding plasma concentrations. The concentration of sparfloxacin in respiratory tissues (pulmonary parenchyma, bronchial wall, and bronchial mucosa) at 2 to 6 hours following standard oral dosing was approximately 3 to 6 times greater than the corresponding concentration in plasma. Concentrations in these respiratory tissues increase at up to 24 hours following dosing. Sparfloxacin is also highly concentrated into alveolar macrophages compared to plasma. Tissue or fluid to plasma sparfloxacin concentration ratios for respiratory tissues and fluids are:

Tissue to Plasma Sparfloxacin Concentration Mean Ratio (%CV)*

Respiratory tissues And fluids	n** value	Time of Collection Postdose 2 to 6 hour		12 to 24 hour	
Alveolar macrophage	6/5	51.8	(88.7%)	68.1	(47.9%)
Epithelial lining fluid	10/10	12.3	(26.7%)	17.6	(35.3%)
Pulmonary parenchyma	8/7	5.9	(15.0%)	15.8	(32.0%)
Bronchial wall	8/7	2.8	(16.0%)	5.7	(25.0%)
Bronchial mucosa	6/5	2.7	(11.5%)	3.1	(11.6%)

* % CV (percent coefficient of variation)

** For tissues with two values, the first n is for 2 to 6 hours and the second n is for 12 to 24 hours.

Mean pleural effusion to plasma concentration ratios were 0.34 and 0.69 at 4 and 20 hours postdose, respectively.

Metabolism: Sparfloxacin is metabolized by the liver, primarily by phase II glucuronidation, to form a glucuronide conjugate. Its metabolism does not utilize or interfere with cytochrome-mediated oxidation, in particular cytochrome P450.

Excretion: The total body clearance and renal clearance of sparfloxacin were 11.4 (±3.5) and 1.5 (±0.5) L/hr, respectively. Sparfloxacin is excreted in both the feces (50%) and urine (50%). Approximately 10% of an orally administered dose is excreted in the urine as unchanged drug in patients with normal renal function. Following a 400-mg loading dose of sparfloxacin, the mean urine concentration 4 hours postdose was in excess of 12.0 μg/mL, and measurable concentrations of active drug persisted through six days for subjects with normal renal function.

The terminal elimination phase half-life ($t_{1/2}$) of sparfloxacin in plasma generally varies between 16 and 30 hours, with a mean $t_{1/2}$of approximately 20 hours. The $t_{1/2}$ is independent of the administered dose, suggesting that sparfloxacin elimination kinetics are linear.

Special Populations: *Geriatric:* The pharmacokinetics of sparfloxacin are not altered in the elderly with normal renal function.

Pediatric: The pharmacokinetics of sparfloxacin in pediatric subjects have not been studied.

Gender: There are no gender differences in the pharmacokinetics of sparfloxacin.

Renal insufficiency: In patients with renal impairment (creatinine clearance <50 mL/min), the terminal elimination half-life of sparfloxacin is lengthened. Single or multiple doses of sparfloxacin in patients with varying degrees of renal impairment typically produce plasma concentrations that are twice those observed in subjects with normal renal function. (See **PRECAUTIONS: General** and **DOSAGE AND ADMINISTRATION**.)

Hepatic insufficiency: The pharmacokinetics of sparfloxacin are not altered in patients with mild or moderate hepatic impairment without cholestasis.

MICROBIOLOGY: Sparfloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. Sparfloxacin exerts its antibacterial activity by inhibiting DNA gyrase, a bacterial topoisomerase. DNA gyrase is an essential enzyme which controls DNA topology and assists in DNA replication, repair, deactivation, and transcription.

Quinolones differ in chemical structure and mode of action from β-lactam antibiotics. Quinolones may, therefore, be active against bacteria resistant to β-lactam antibiotics.

Although cross-resistance has been observed between sparfloxacin and other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to sparfloxacin.

In vitro tests show that the combination of sparfloxacin and rifampin is antagonistic against *Staphylococcus aureus*.

Sparfloxacin 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

Staphylococcus aureus
Streptococcus pneumoniae (penicillin-susceptible strains)

Aerobic gram-negative microorganisms
Enterobacter cloacae
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis

Other microorganisms
Chlamydia pneumoniae
Mycoplasma pneumoniae

The following *in vitro* data are available, **but their clinical significance is unknown:**

Sparfloxacin exhibits *in vitro* minimal inhibitory concentrations (MICs) of 1 µg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of sparfloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-positive microorganisms
Streptococcus agalactiae
Streptococcus pneumoniae (penicillin-resistant strains)
Streptococcus pyogenes
Viridans group streptococci

Aerobic gram-negative microorganisms
Acinetobacter anitratus
Acinetobacter lwoffi
Citrobacter diversus

Enterobacter aerogenes
Klebsiella oxytoca
Legionella pneumophila
Morganella morganii
Proteus mirabilis
Proteus vulgaris

SUSCEPTIBILITY TESTS: Dilution Techniques: Quantitative methods are used to determine antimicrobial minimal 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 sparfloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing aerobic microorganisms other than *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Streptococcus pneumoniae:*

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

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae:*[a]

MIC (µg/mL)	**Interpretation**
≤0.25	Susceptible (S)

[a]These interpretive standards are applicable only to broth microdilution susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using Haemophilus Test Medium[1].

The current absence of data on resistant strains precludes defining any categories other than "Susceptible." Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus pneumoniae*:[b]

MIC (µg/mL)	Interpretation
≤0.5	Susceptible (S)

[b] These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

The current absence of data on resistant strains precludes defining any categories other than "Susceptible." Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration 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 a 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 concentration 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 sparfloxacin powder should provide the following MIC values:

Microorganism	MIC Range (µg/mL)
Enterococcus faecalis ATCC 29212	0.12-0.5
Escherichia coli ATCC 25922	0.004-0.016
Haemophilus influenzae ATCC 49247[a]	0.004-0.016
Staphylococcus aureus ATCC 29213	0.03-0.12
Streptococcus pneumoniae ATCC 49619[b]	0.12-0.5

[a] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using Haemophilus Test Medium (HTM)[1].

[b] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a 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 5-µg sparfloxacin to test the susceptibility of microorganisms to sparfloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-µg sparfloxacin disk should be interpreted according to the following criteria:

For aerobic microorganisms other than *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Streptococcus pneumoniae:*

Zone Diameter (mm)	Interpretation
≥19	Susceptible (S)
16-18	Intermediate (I)
≤15	Resistant (R)

Haemophilus influenzae and *Haemophilus parainfluenzae* should not be tested by diffusion techniques. An MIC should be determined for these isolates.

For *Streptococcus pneumoniae*:[a]

Zone Diameter (mm)	Interpretation
≥19	Susceptible (S)

[a] These zone diameter standards for *Streptococcus pneumoniae* apply only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2.

The current absence of data on resistant strains precludes any category other than "Susceptible." Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for sparfloxacin.

As with standard dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5-µg sparfloxacin disk should provide the following zone diameters in these laboratory quality control strains:

Microorganism	Zone Diameter (mm)
Escherichia coli ATCC 25922	30-38
Staphylococcus aureus ATCC 25923	27-33
Streptococcus pneumoniae ATCC 49619 [a]	21-27

[a] These quality control limits apply to tests conducted with *S. pneumoniae* ATCC 49619 using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.

INDICATIONS AND USAGE: Zagam (sparfloxacin) is indicated for the treatment of adults (≥ 18 years of age) with the following infections caused by susceptible strains of the designated microorganisms:

Community-acquired pneumonia caused by *Chlamydia pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Mycoplasma pneumoniae,* or *Streptococcus pneumoniae*

Acute bacterial exacerbations of chronic bronchitis caused by *Chlamydia pneumoniae, Enterobacter cloacae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae, Klebsiella pneumoniae*, *Moraxella catarrhalis*, *Staphylococcus aureus,* or *Streptococcus pneumoniae*

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing the infection and to determine their susceptibility to sparfloxacin. Therapy with sparfloxacin may be initiated before results of these tests are known; once results become available, appropriate therapy should be selected. Culture and susceptibility testing performed periodically during therapy will provide information on the continued susceptibility

of the pathogen to the antimicrobial agent and also on the possible emergence of bacterial resistance.

CONTRAINDICATIONS: Sparfloxacin is contraindicated for individuals with a history of hypersensitivity or photosensitivity reactions.

Torsade de pointes has been reported in patients receiving sparfloxacin concomitantly with disopyramide and amiodarone. Consequently, sparfloxacin is contraindicated for individuals receiving these drugs as well as other QT_c-prolonging antiarrhythmic drugs reported to cause torsade de pointes, such as class Ia antiarrhythmic agents (*e.g.*, quinidine, procainamide), class III antiarrhythmic agents (*e.g.*, sotalol), and bepridil. Sparfloxacin is contraindicated in patients with known QT_c prolongation or in patients being treated concomitantly with medications known to produce an increase in the QT_c interval and/or torsade de pointes (*e.g.*, terfenadine). (See **WARNINGS** and **PRECAUTIONS**.)

It is essential to avoid exposure to the sun, bright natural light, and UV rays throughout the entire duration of treatment and for 5 days after treatment is stopped. Sparfloxacin is contraindicated in patients whose life-style or employment will not permit compliance with required safety precautions concerning phototoxicity. (See **WARNINGS** and **PRECAUTIONS**.)

WARNINGS: MODERATE TO SEVERE PHOTOTOXIC REACTIONS HAVE OCCURRED IN PATIENTS EXPOSED TO DIRECT OR INDIRECT SUNLIGHT OR TO ARTIFICIAL ULTRAVIOLET LIGHT (*e.g.*, SUNLAMPS) DURING OR FOLLOWING TREATMENT. THESE REACTIONS HAVE ALSO OCCURRED IN PATIENTS EXPOSED TO SHADED OR DIFFUSE LIGHT, INCLUDING EXPOSURE THROUGH GLASS OR DURING CLOUDY WEATHER. PATIENTS SHOULD BE ADVISED TO DISCONTINUE SPARFLOXACIN THERAPY AT THE FIRST SIGNS OR SYMPTOMS OF A PHOTOTOXICITY REACTION SUCH AS A SENSATION OF SKIN BURNING, REDNESS, SWELLING, BLISTERS, RASH, ITCHING, OR DERMATITIS.

The overall incidence of drug related phototoxicity in the 1585 patients who received sparfloxacin during clinical trials with recommended dosage was 7.9% (n=126). Phototoxicity ranged from mild 4.1% (n=65) to moderate 3.3% (n=52) to severe 0.6% (n=9), with severe defined as involving at least significant curtailment of normal daily activity. The frequency of phototoxicity reactions characterized by blister formation was 0.8% (n=13) of which 3 were severe. The discontinuation rate due to phototoxicity independent of drug relationship was 1.1% (n=17).

As with some other types of phototoxicity, there is the potential for exacerbation of the reaction on re-exposure to sunlight or artificial ultraviolet light prior to complete recovery from the reaction. In a few cases, recovery from

phototoxicity reactions was prolonged for several weeks. In rare cases, reactions have recurred up to several weeks after stopping sparfloxacin therapy.

EXPOSURE TO DIRECT AND INDIRECT SUNLIGHT (EVEN WHEN USING SUNSCREENS OR SUNBLOCKS) SHOULD BE AVOIDED WHILE TAKING SPARFLOXACIN AND FOR FIVE DAYS FOLLOWING THERAPY. SPARFLOXACIN THERAPY SHOULD BE DISCONTINUED IMMEDIATELY AT THE FIRST SIGNS OR SYMPTOMS OF PHOTOTOXICITY.

These phototoxic reactions have occurred with and without the use of sunscreens or sunblocks and have been associated with a single dose of sparfloxacin. However, a study in healthy volunteers has demonstrated that some sunscreen products, specifically those active in blocking UVA spectrum wavelengths (those containing the active ingredients octocrylene or Parsol® 1789), can moderate the photosensitizing effect of sparfloxacin. However, many over-the-counter sunscreens do not provide adequate UVA protection.

Increases in the QT_c interval have been observed in healthy volunteers treated with sparfloxacin. After a single loading dose of 400 mg, a mean increase in QT_c interval of 11 msec (2.9%) is seen; at steady-state the mean increase is 7 msec (1.9%). The magnitude of the QT_c effect does not increase with repeated administration, and the QT_c returns to baseline within 48 hours of the last dose. In

clinical trials involving 1489 patients with a baseline QT_c measurement, the mean prolongation at steady-state was 10 msec (2.5%); 0.7% of patients had a QT_c interval greater than 500 msec; however, no arrhythmic effects were seen.

In a covariate analysis, age did not have a statistically significant contribution to the change in QT_c recorded in patients taking sparfloxacin. However, in controlled clinical trials, QT_c interval prolongation was more frequently reported as an adverse event in patients ≥65 years of age than in younger patients. In these clinical trials, QT_c interval prolongation was reported more frequently as an adverse event (defined as QT_c ≥0.440 sec or ≥15% change from baseline) in elderly patients treated with sparfloxacin than in elderly patients treated with a comparator drug. During post marketing surveillance, cardiovascular events including torsades de pointes and other arrhythmias were more frequent in the elderly than in younger patients treated with sparfloxacin although a history of underlying cardiac disease in this population was more common. Sparfloxacin is contraindicated in patients with known QT_c prolongation (see **CONTRAINDICATIONS**).

THE SAFETY AND EFFECTIVENESS OF SPARFLOXACIN IN PEDIATRIC PATIENTS, ADOLESCENTS (UNDER THE AGE OF 18 YEARS), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See **PRECAUTIONS: Pediatric Use, Pregnancy,** and **Nursing Mothers** subsections.)

Sparfloxacin has been shown to cause arthropathy in immature dogs when given in oral doses of 25 mg/kg/day (approximately 1.9 times the highest human dose on a mg/m^2 basis) for seven consecutive days. Examination of the weight-bearing joints of the dogs revealed small erosive lesions of the cartilage. Other quinolones also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species.

Convulsions and toxic psychoses have been reported in patients receiving quinolones, including sparfloxacin. Quinolones may also cause increased intracranial pressure and central nervous system stimulation which may lead to tremors, restlessness/agitation, anxiety/nervousness, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving sparfloxacin, the drug should be discontinued and appropriate measures instituted. As with other quinolones, sparfloxacin should be used with caution in patients with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (*e.g.*, severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (*e.g.*, certain drug therapy, renal dysfunction). Cases of seizure associated with hypoglycemia have been reported. (See **PRECAUTIONS: General Information for Patients, Drug Interactions** and **ADVERSE REACTIONS.**)

Serious and occasionally fatal hypersensitivity (including anaphylactoid or anaphylactic) reactions, some following the first dose, have been reported in patients receiving quinolones. Some reactions were accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat, or facial edema), airway obstruction (including bronchospasm, shortness of breath, and acute respiratory distress), dyspnea, urticaria, and/or itching. Only a few patients had a history of previous hypersensitivity reactions. If an allergic reaction to sparfloxacin occurs, the drug should be discontinued immediately. Serious acute hypersensitivity reactions may require immediate treatment with epinephrine, and other resuscitative measures including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, including intubation, as clinically indicated.

Serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with quinolones. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following: fever, rash or severe dermatologic reactions (*e.g.*, toxic epidermal necrolysis, Stevens-Johnson Syndrome); vasculitis; arthralgia; myalgia; serum sickness; allergic pneumonitis; interstitial nephritis; acute renal insufficiency or failure; hepatitis; jaundice; acute hepatic necrosis or failure; anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic

abnormalities. The drug should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity and supportive measures instituted. (See **PRECAUTIONS: Information for Patients** and **ADVERSE REACTIONS.**)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including sparfloxacin, 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 one 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 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.

Ruptures of the shoulder, hand, and Achilles tendons that required surgical repair or resulted in prolonged disability have been reported with sparfloxacin and other quinolones. Sparfloxacin should be discontinued if the patient experiences pain,

inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been confidently excluded. Tendon rupture can occur at any time during or after therapy with sparfloxacin.

PRECAUTIONS: General: Adequate hydration of patients receiving sparfloxacin should be maintained to prevent the formation of a highly concentrated urine.

Administer sparfloxacin with caution in the presence of renal insufficiency. Careful clinical observation and appropriate laboratory studies should be performed prior to and during therapy since elimination of sparfloxacin may be reduced. Adjustment of the dosage regimen is necessary for patients with impaired renal function-creatinine clearance <50 mL/min. (See **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**.)

Avoid the concomitant prescription of medications known to prolong the QT_c interval, *e.g.*, erythromycin, terfenadine, astemizole, cisapride, pentamidine, tricyclic antidepressants, some antipsychotics including phenothiazines. (See **CONTRAINDICATIONS**.) Sparfloxacin is not recommended for use in patients with pro-arrhythmic conditions (*e.g.*, hypokalemia, significant bradycardia, congestive heart failure, myocardial ischemia, and atrial fibrillation).

Moderate to severe phototoxicity reactions have been observed in patients exposed to direct sunlight while receiving drugs in this class. Excessive exposure to

sunlight should be avoided. In clinical trials with sparfloxacin, phototoxicity was observed in approximately 7% of patients. Therapy should be discontinued if phototoxicity (*e.g.*, a skin eruption) occurs.

As with other quinolones, sparfloxacin should be used with caution in any patient with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (*e.g.*, severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (*e.g.*, certain drug therapy, renal dysfunction). (See **WARNINGS** and **Drug Interactions**.)

Information for Patients: *Patients should be advised:*

- to avoid exposure to direct or indirect sunlight (including through glass, while using sunscreens and sunblocks, reflected sunlight, and cloudy weather) and exposure to artificial ultraviolet light (*e.g.*, sunlamps) during treatment with sparfloxacin and for five days after therapy. If brief exposure to the sun cannot be avoided, patients should cover as much of their skin as possible with clothing;

- to discontinue sparfloxacin therapy at the first sign or symptom of phototoxicity reaction such as a sensation of skin burning, redness, swelling, blisters, rash, itching or dermatitis;

• that a patient who has experienced a phototoxic reaction with sparfloxacin should also be advised to avoid further exposure to sunlight and artificial ultraviolet light until the phototoxicity reaction has resolved and he or she has completely recovered from the reaction or for five days whichever is longer. In rare cases, reactions have recurred up to several weeks after stopping sparfloxacin therapy;

• that sparfloxacin may cause neurologic adverse effects (*e.g.*, dizziness, lightheadedness) and that patients should know how they react to sparfloxacin before they operate an automobile or machinery or engage in other activities requiring mental alertness and coordination. (See **WARNINGS** and **ADVERSE REACTIONS**.);

• to discontinue treatment and inform their physician if they experience pain, inflammation, or rupture of a tendon, and to rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been confidently excluded;

• that sparfloxacin can be taken with food or milk or caffeine-containing products;

• that mineral supplements or vitamins with iron, or zinc, or calcium may be taken 4 hours after sparfloxacin administration;

• that sucralfate or magnesium- and aluminum-containing antacids or Videx® (Didanosine), chewable/buffered tablets or the pediatric powder for oral solution may be taken 4 hours after sparfloxacin administration. (See **PRECAUTIONS: Drug Interactions**.);

• that sparfloxacin may be associated with hypersensitivity reactions, even following the first dose, and to discontinue the drug at the first sign of a skin rash or other allergic reaction;

• to drink fluids liberally;

• that convulsions have been reported in patients taking quinolones, including sparfloxacin, and to notify their physician before taking this drug if there is a history of this condition.

Drug Interactions: *Digoxin:* Sparfloxacin has no effect on the pharmacokinetics of digoxin.

Methylxanthines: Sparfloxacin does not increase plasma theophylline concentrations. Since there is no interaction with theophylline, interaction with other methylxanthines such as caffeine is unlikely.

Warfarin: Sparfloxacin does not increase the anti-coagulant effect of warfarin.

Cimetidine: Cimetidine does not affect the pharmacokinetics of sparfloxacin.

Antacids and Sucralfate: Aluminum and magnesium cations in antacids and sucralfate form chelation complexes with sparfloxacin. The oral bioavailability of sparfloxacin is reduced when an aluminum-magnesium suspension is administered between 2 hours before and 2 hours after sparfloxacin administration. Similarly, the oral bioavailability of sparfloxacin may be reduced when Videx®, (Didanosine), chewable/buffered tablets or the pediatric powder for oral solution is administered between 2 hours before and 2 hours after sparfloxacin administration. The oral bioavailability of sparfloxacin is not reduced when the aluminum-magnesium suspension is administered 4 hours following sparfloxacin administration.

Zinc/iron salts: Absorption of quinolones is reduced significantly by these preparations. These products may be taken 4 hours after sparfloxacin administration.

Probenecid: Probenecid does not alter the pharmacokinetics of sparfloxacin.

Drug/Laboratory Test Interactions: Sparfloxacin therapy may produce false-negative culture results for *Mycobacterium tuberculosis* by suppression of mycobacterial growth.

Carcinogenesis, Mutagenesis, Impairment of Fertility: *Carcinogenesis:* Sparfloxacin was not carcinogenic in mice or rats when administered for 104 weeks at daily oral doses 3.5 - 6.2 times greater than the maximum human dose (400 mg), respectively, based upon mg/m^2. These doses corresponded to plasma concentrations approximately equal to (mice) and 2.2 times greater than (rats) maximum human plasma concentrations.

In a study of repeated exposure (5 days per week for 40 weeks) of hairless albino mice (SKH-1) to a low dose (0.272 Caucasian human minimal erythema dose [MED]) of solar simulated UV radiation, skin tumors were induced with a median onset time of 43 weeks. As expected for this model, the gross appearance of the tumors in this study was consistent with squamous cell carcinoma or its precursors. When sparfloxacin (6.0 or 12.5 mg/kg/day) was administered by the oral route, the median tumor onset time was reduced to 38 and 32 weeks, respectively. This reduction in median onset time was similar to that observed when mice were exposed to a higher dose (0.476 Caucasian human MED) of solar simulated UV radiation alone. At a dose level of 12.5 mg/kg/day, mice had skin sparfloxacin concentrations (± SD) of approximately 1.8 µg/g (± 0.26, N=6). Following a 400 mg dose of sparfloxacin, skin levels measured in human subjects averaged 5.5 µg/g (± 6.5, N=11). A similar effect on the time to the development of skin tumors has been observed in this mouse strain with some other fluoroquinolone antibiotics. The clinical significance of these findings to humans is unknown.

Mutagenesis: Sparfloxacin was not mutagenic in *Salmonella typhimurium* TA98, TA100, TA1535, or TA1537, in *Escherichia coli* strain WP2 uvrA, nor in Chinese hamster lung cells. Sparfloxacin and other quinolones have been shown to be mutagenic in *Salmonella typhimurium* strain TA102 and to induce DNA repair in *Escherichia coli*, perhaps due to their inhibitory effect on bacterial DNA gyrase. Sparfloxacin induced chromosomal aberrations in Chinese hamster lung cells *in vitro* at cytotoxic concentrations; however, no increase in chromosomal aberrations or micronuclei in bone marrow cells was observed after sparfloxacin was administered orally to mice.

When Chinese hamster ovary cells were incubated with sparfloxacin in the presence of solar simulated UV radiation, chromosome aberrations were induced at concentrations of sparfloxacin that were not associated with aberrations in the absence of UV. The low level of UV used in the experiment, approximately 375 mJ/cm^2, was not, by itself, associated with chromosome aberrations, while the high level of UV used in the experiment, approximately 750 mJ/cm^2, induced fewer aberrations than sparfloxacin plus low or high dose UV.

Impairment of Fertility: Sparfloxacin had no effect on the fertility or reproductive performance of male or female rats at oral doses up to 15.4 times the maximum human dose (400 mg) based upon mg/m^2 (equivalent to approximately 12 times the maximum human plasma concentration).

Pregnancy: *Teratogenic Effects: Pregnancy Category C:* Reproduction studies performed in rats, rabbits, and monkeys at oral doses 6.2, 4.4, and 2.6 times higher than the maximum human dose, respectively, based upon mg/m^2 (corresponding to plasma concentrations 4.5- and 6.5-fold higher than in humans in the monkey and rat, respectively) did not reveal any evidence of teratogenic effects. At these doses, sparfloxacin was clearly maternally toxic to the rabbit and monkey with evidence of slight maternal toxicity observed in the rat. When administered to pregnant rats at clearly maternally toxic doses (≥9.3 times the maximum human dose based upon mg/m^2), sparfloxacin induced a dose-dependent increase in the incidence of fetuses with ventricular septal defects. Among the three species tested, this effect was specific to the rat. There are, however, no adequate and well-controlled studies in pregnant women. Sparfloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See **WARNINGS**.)

Nursing Mothers: Sparfloxacin is excreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking sparfloxacin, 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: Safety and effectiveness in pediatric patients and adolescents under the age of 18 years have not been established. Quinolones, including sparfloxacin,

cause arthropathy and osteochondrosis in juvenile animals of several species. (See **WARNINGS**.)

Geriatric Use: In controlled clinical trials conducted in the United States and Europe, sparfloxacin tablets have been administered to approximately 458 elderly (∃65 years of age) patients. It is known that the QT_c interval increases with increasing age. In a covariate analysis, age did not have a statistically significant contribution to the change in QT_c recorded in patients taking sparfloxacin. However, in controlled clinical trials, QT_c interval prolongation was more frequently reported as an adverse event in patients ∃65 years of age than in younger patients. In addition, QT_c interval prolongation was reported more frequently as an adverse event (defined as QT_c ∃0.440 sec or ∃15% change from baseline) in sparfloxacin treated elderly patients (7/314) than elderly patients treated with a comparator drug (0/301). Finally, the majority of patients with postmarketing cardiovascular events were elderly; however, it is not possible to exclude the roles of other contributing factors such as underlying cardiovascular diseases and concomitant medications. There were no other apparent overall differences in safety and efficacy observed between the elderly and younger individuals in controlled clinical trials. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Sparfloxacin is known to be excreted renally and the risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be

useful to monitor renal function. (See **CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION** and **WARNINGS**.)

The pharmacokinetic parameters of sparfloxacin in the elderly were consistent with those observed in normal healthy subjects. (See **CLINICAL PHARMACOLOGY:Special Populations**.)

ADVERSE REACTIONS: In clinical trials, most of the adverse events were mild to moderate in severity and transient in nature. During clinical investigations with the recommended dosage, 1585 patients received sparfloxacin and 1331 patients received a comparator. The discontinuation rate due to adverse events was 6.6% for sparfloxacin versus 5.6% for cefaclor, 14.8% for erythromycin, 8.9% for ciprofloxacin, 7.4% for ofloxacin, and 8.3% for clarithromycin.

The most frequently reported events (remotely, possibly, or probably drug related with an incidence of ≥1%) among sparfloxacin treated patients in the US phase 3 clinical trials with the recommended dosage were: photosensitivity reaction (7.9%), diarrhea (4.6%), nausea (4.3%), headache (4.2%), dyspepsia (2.3%), dizziness (2.0%), insomnia (1.9%), abdominal pain (1.8%), pruritus (1.8%), taste perversion (1.4%), and QT_c interval prolongation (1.3%), vomiting (1.3%), flatulence (1.1%), and vasodilatation (1.0%).

In US phase 3 clinical trials of shorter treatment duration than the recommended dosage, the most frequently reported events (incidence ≥1%, remotely, possibly, or probably drug related) were: headache (8.1%), nausea (7.6%), dizziness (3.8%), photosensitivity reaction (3.6%), pruritus (3.3%), diarrhea (3.2%), vaginal moniliasis (2.8%), abdominal pain (2.4%), asthenia (1.7%), dyspepsia (1.6%), somnolence (1.5%), dry mouth (1.4%), and rash (1.1%).

Additional possibly or probably related events that occurred in less than 1% of all patients enrolled in US phase 3 clinical trials are listed below:

BODY AS A WHOLE: fever, chest pain, generalized pain, allergic reaction, cellulitis, back pain, chills, face edema, malaise, accidental injury, anaphylactoid reaction, infection, mucous membrane disorder, neck pain, rheumatoid arthritis;

CARDIOVASCULAR: palpitation, electrocardiogram abnormal, hypertension, tachycardia, sinus bradycardia, PR interval shortened, angina pectoris, arrhythmia, atrial fibrillation, atrial flutter, complete AV block, first degree AV block, second degree AV block, cardiovascular disorder, hemorrhage, migraine, peripheral vascular disorder, supraventricular extrasystoles, ventricular extrasystoles, postural hypotension;

GASTROINTESTINAL: constipation, anorexia, gingivitis, oral moniliasis, stomatitis, tongue disorder, tooth disorder, gastroenteritis, increased appetite, mouth ulceration, flatulence, vomiting;

HEMATOLOGIC: cyanosis, ecchymosis, lymphadenopathy;

METABOLISM: gout, peripheral edema, thirst;

MUSCULOSKELETAL: arthralgia, arthritis, joint disorder, myalgia;

CENTRAL NERVOUS SYSTEM: paresthesia, hypesthesia, nervousness, somnolence, abnormal dreams, dry mouth, depression, tremor, anxiety, confusion, hallucinations, hyperesthesia, hyperkinesia, sleep disorder, hypokinesia, vertigo, abnormal gait, agitation, lightheadedness, emotional lability, euphoria, abnormal thinking, amnesia, twitching;

RESPIRATORY: asthma, epistaxis, pneumonia, rhinitis, pharyngitis, bronchitis, hemoptysis, sinusitis, cough increased, dyspnea, laryngismus, lung disorder, pleural disorder;

SKIN/HYPERSENSITIVITY: rash, maculopapular rash, dry skin, herpes simplex, sweating, urticaria, vesiculobullous rash, exfoliative dermatitis, acne, alopecia,

angioedema, contact dermatitis, fungal dermatitis, furunculosis, pustular rash, skin discoloration, herpes zoster, petechial rash;

SPECIAL SENSES: ear pain, amblyopia, photophobia, tinnitus, conjunctivitis, diplopia, abnormality of accommodation, blepharitis, ear disorder, eye pain, lacrimation disorder, otitis media;

UROGENITAL: vaginitis, dysuria, breast pain, dysmenorrhea, hematuria, menorrhagia, nocturia, polyuria, urinary tract infection, kidney pain, leukorrhea, metrorrhagia, vulvovaginal disorder.

Laboratory Changes: In the US phase 3 clinical trials, with the recommended dosage, the most frequently (incidence ≥1%) reported changes in laboratory parameters listed as adverse events, regardless of relationship to drug, were: elevated ALT (SGPT) (2.0%), AST (SGOT) (2.3%), and white blood cells (1.1%).

Increases for the following laboratory tests were reported in less than 1% of all patients enrolled in clinical trials: alkaline phosphatase, serum amylase, aPTT, blood urea nitrogen, calcium, creatinine, eosinophils, serum lipase, monocytes, neutrophils, total bilirubin, urine glucose, urine protein, urine red blood cells, and urine white blood cells.

Decreases for the following laboratory tests were reported in less than 1% of all patients enrolled in clinical trials: albumin, creatinine clearance, hematocrit, hemoglobin, lymphocytes, phosphorus, red blood cells, and sodium.

Increases and decreases for the following laboratory tests were reported in less than 1% of all patients in clinical trials: blood glucose, platelets, potassium, and white blood cells.

Postmarketing Adverse Events: The following are additional adverse events (regardless of relationship to drug) reported from worldwide postmarketing experience with sparfloxacin or other quinolones: acidosis, acute renal failure, agranulocytosis, albuminuria, anaphylactic shock, angioedema, anosmia, ataxia, bullous eruption, candiduria, cardiopulmonary arrest, cerebral thrombosis, convulsions, crystalluria, dysgeusia, dysphasia, ebrious feeling, embolism, erythema nodosum, exacerbation of myasthenia gravis, gastralgia, hemolytic anemia, hepatic failure, hepatic necrosis, hepatitis, hiccough, hyperpigmentation, interstitial nephritis, interstitial pneumonia, intestinal perforation, jaundice, laryngeal or pulmonary edema, manic reaction, numbness, nystagmus, painful oral mucosa, pancreatitis, pancytopenia, phobia, prolongation of prothrombin time, pseudomembranous colitis, Quincke's edema, renal calculi, rhabdomyolysis, sensory disturbance, Stevens-Johnson syndrome, squamous cell carcinoma, tendonitis, tendon rupture, tremor, thrombocytopenia, thrombocytopenia purpura, torsades de pointes, toxic epidermal necrolysis, toxic psychosis, urinary retention, uveitis, vaginal candidiasis, vasculitis.

Laboratory changes: elevation of serum triglycerides, serum cholesterol, blood glucose, serum potassium, decrease in WBC counts, RBC counts, hemoglobin level, hematocrit level, thrombocyte counts, elevation in GOT, GPT, ALP, LDH, γ-GTP, total bilirubin.

OVERDOSAGE: In case of overdosage, the patient should be monitored in a suitably equipped medical facility and advised to avoid sun exposure for five days. ECG monitoring is recommended due to the possible prolongation of the QT_c interval. There is no known antidote for sparfloxacin overdosage.

It is not known whether sparfloxacin is dialyzable.

Single doses of sparfloxacin were relatively non-toxic via the oral route of administration in mice, rats, and dogs. No deaths occurred within a 14-day post-treatment observation period at the highest oral doses tested, up to 5000 mg/kg in either rodent species, or up to 600 mg/kg in the dog. Clinical signs observed included inactivity in mice and dogs, diarrhea in both rodent species, and vomiting, salivation, and tremors in dogs.

DOSAGE AND ADMINISTRATION: Zagam (sparfloxacin) can be taken with or without food.

Antacids containing magnesium and aluminum or sucralfate or Videx®, (Didanosine), chewable/buffered tablets or the pediatric powder for oral solution may be taken 4 hours after administration of Zagam (sparfloxacin).

The recommended daily dose of Zagam in patients with normal renal function is two 200-mg tablets taken on the first day as a loading dose. Thereafter, one 200-mg tablet should be taken every 24 hours for a total of 10 days of therapy (11 tablets).

The recommended daily dose of Zagam in patients with renal impairment (creatinine clearance <50 mL/min) is two 200-mg tablets taken on the first day as a loading dose. Thereafter, one 200-mg tablet should be taken every 48 hours for a total of 9 days of therapy (6 tablets).

CLINICAL STUDIES:

Community-Acquired Pneumonia Studies

In two controlled clinical studies of community-acquired pneumonia conducted in the United States, sparfloxacin was compared to erythromycin and cefaclor. The patient clinical success and pathogen eradication rates for sparfloxacin were equivalent to those of the comparators. In these studies, the following pathogen eradication rates/presumed pathogen eradication rates were obtained:

Organism	Sparfloxacin		Erythromycin*		Cefaclor	
C. pneumoniae	19/22	(86.4%)	3/4	(75%)	5/5	(100%)
H. influenzae	20/24	(83.3%)	0		25/31	(80.6%)
H. parainfluenzae	61/63	(96.8%)	4/4	(100%)	31/41	(75.6%)
M. catarrhalis	7/8	(87.5%)	4/4	(100%)	5/6	(83.3%)
M. pneumoniae	36/39	(92.3%)	15/15	(100%)	20/24	(83.3%)
S. pneumoniae	39/41	(95.1%)	10/11	(90%)	16/17	(94.1%)

*Pathogen numbers were smaller since many of the strains were intrinsically resistant to erythromycin.

Safety

The following table lists possibly and probably drug-related adverse events that occurred in these studies at an incidence of ≥2%:

Event	Sparfloxacin n=387		Erythromycin n=209		Cefaclor n=162	
Abdominal Pain	6	(1.6%)	18	(8.6%)	2	(1.2%)
Photosensitivity Reaction	16	(4.1%)	0		1	(0.6%)
QT Interval Prolonged	8	(2.1%)	2	(1.0%)	1	(0.6%)
Sinus Bradycardia	2	(0.5%)	6	(2.9%)	0	
Diarrhea	15	(3.9%)	33	(15.8%)	7	(4.3%)
Flatulence	0		5	(2.4%)	0	
Nausea	11	(2.8%)	32	(15.3%)	4	(2.5%)
Vomiting	10	(2.6%)	15	(7.2%)	1	(0.6%)
Insomnia	6	(1.6%)	5	(2.4%)	0	

Acute Bacterial Exacerbations of Chronic Bronchitis Study

In a controlled clinical study of acute bacterial exacerbations of chronic bronchitis conducted in the United States, sparfloxacin was compared to ofloxacin. In this study, the following pathogen eradication rates were obtained:

Organism	Sparfloxacin		Ofloxacin	
H. parainfluenzae	102/107	(95.3%)	89/93	(95.7%)
H. influenzae	49/55	(89.1%)	60/63	(95.2%)
C. pneumoniae	35/43	(81.4%)	35/39	(89.7%)

M. catarrhalis	33/35	(94.3%)	30/31	(96.8%)
S. pneumoniae	30/34	(88.2%)	20/22	(90.9%)
S. aureus	16/19	(84.2%)	13/14	(92.9%)
K. pneumoniae	17/17	(100%)	15/17	(88.2%)
E. cloacae	12/13	(92.3%)	12/15	(80%)

Safety

The following table lists possibly and probably drug-related adverse events that occurred in the study at an incidence of ≥2% for either compound.

Event	**Sparfloxacin** (n=395)		**Ofloxacin** (n=403)	
Headache	11	(2.8%)	6	(1.5%)
Photosensitivity Reaction	29	(7.3%)	3	(0.7%)
Diarrhea	6	(1.5%)	9	(2.2%)
Dyspepsia	8	(2.0%)	14	(3.5%)
Nausea	16	(4.1%)	29	(7.2%)
Dizziness	12	(3.0%)	10	(2.5%)
Insomnia	4	(1.0%)	46	(11.4%)
Taste Perversion	10	(2.5%)	10	(2.5%)

HOW SUPPLIED:

Strength	**Size**	**NDC 62794-**	**Description / Markings**
200 mg	Blister Pack of 11 (RespiPac™)	011-11	A white film-coated, round bi-convex, tablet debossed with **B** over **11** on one side of the tablet and blank on the other side.
	Bottle of 55	011-55	

Store at Controlled Room Temperature 20 to 25°C (68 to 77°F) [see USP].

Keep out of the reach of children.

ANIMAL PHARMACOLOGY: Sparfloxacin and other quinolones have been shown to cause arthropathy in juvenile animals of most species tested. (See **WARNINGS.**)

Sparfloxacin had no convulsive activity in mice when administered alone or in combination with the nonsteroidal anti-inflammatory agents ketoprofen, or naproxen.

References:

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically—Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December 1993.

2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests—Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December 1993.

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