FORTECIN
(Co-Amoxiclav)

375 mg, 625 mg & 1gm Tablets

156.25mg/5ml & 312.5mg/5ml suspension

COMPOSITION

FORTECIN 375 mg tablets:
Each tablet contains Amoxicillin Trihydrate B.P. equivalent to 250 mg Amoxicillin base and Potassium Clavulanate equivalent 125 mg Clavulanic Acid
FORTECIN 625 mg tablets:
Each tablet contains Amoxicillin Trihydrate B.P. equivalent to 500 mg Amoxicillin base and Potassium Clavulanate equivalent 125 mg Clavulanic Acid
FORTECIN 1 gm tablets:
Each tablet contains Amoxicillin Trihydrate B.P. equivalent to 875 mg Amoxicillin base and Potassium Clavulanate equivalent 125 mg Clavulanic Acid
FORTECIN 156.25 mg suspension:
Each 5 ml contains Amoxicillin Trihydrate B.P. equivalent to 125 mg Amoxicillin base and Potassium Clavulanate equivalent 31.25 mg Clavulanic Acid
FORTECIN 312.5 mg suspension:
Each 5 ml contains Amoxicillin Trihydrate B.P. equivalent to 250 mg Amoxicillin base and Potassium Clavulanate equivalent 62.50 mg Clavulanic Acid

THERAPEUTIC INDICATIONS

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Co-Amoxiclav (amoxicillin/clavulanate potassium) and other antibacterial drugs, Co-Amoxiclav should be used only to treat 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.
Co-Amoxiclav is a combination penicillin-class antibacterial and beta-lactamase inhibitor indicated in the treatment of infections due to susceptible isolates of the designated bacteria in the conditions listed below*:

Lower Respiratory Tract Infections
caused by beta-lactamase–producing isolates of *Haemophilus influenzae and Moraxella catarrhalis*.

Acute Bacterial Otitis Media
caused by beta-lactamase–producing isolates of *H. influenzae and M. catarrhalis*.

Sinusitis
caused by beta-lactamase–producing isolates of *H. influenzae and M. catarrhalis*.

Skin and Skin Structure Infections
caused by beta-lactamase–producing isolates of *Staphylococcus aureus, Escherichia coli, and Klebsiella species.*

Urinary Tract Infections
caused by beta-lactamase–producing isolates of *E. coli, Klebsiella species, and Enterobacter species*.

Limitations of Use
When susceptibility test results show susceptibility to amoxicillin, indicating no beta-lactamase production, Co-Amoxiclav should not be used.

DOSAGE AND ADMINISTRATION

Co-Amoxiclav may be taken without regard to meals; however, absorption of clavulanate potassium is enhanced when Co-Amoxiclav is administered at the start of a meal. To minimize the potential for gastrointestinal intolerance, Co-Amoxiclav should be taken at the start of a meal.

Adults

The usual adult dose is one 500-mg tablet of Co-Amoxiclav every 12 hours or one 250-mg tablet of Co-Amoxiclav every 8 hours. For more severe infections and infections of the respiratory tract, the dose should be one 875-mg tablet of Co-Amoxiclav every 12 hours or one 500-mg tablet of Co-Amoxiclav every 8 hours. Adults who have difficulty swallowing may be given the 125 mg/5 mL or 250 mg/5 mL suspension in place of the 500-mg tablet.

Two 250-mg tablets of Co-Amoxiclav should *not* be substituted for one 500-mg tablet of Co-Amoxiclav. Since both the 250-mg and 500-mg tablets of Co-Amoxiclav contain the same amount of clavulanic acid (125 mg, as the potassium salt), two 250-mg tablets are not equivalent to one 500-mg tablet of Co-Amoxiclav

Pediatric Patients

Based on the amoxicillin component, Co-Amoxiclav should be dosed as follows:

Neonates and Infants Aged <12 weeks (<3 months): The recommended dose of Co-Amoxiclav is 30 mg/kg/day divided every 12 hours, based on the amoxicillin component. Experience with the 200 mg/5 mL formulation in this age group is limited, and thus, use of the 125 mg/5 mL oral suspension is recommended.

Patients Aged 12 weeks (3 months) and Older: See dosing regimens provided in Table 1. The every 12 hour regimen is recommended as it is associated with significantly less diarrhea. Duration of therapy studied and recommended for acute otitis media is 10 days.

Table 1: Dosing in Patients Aged 12 weeks (3 months) and Older

INFECTION	DOSING REGIMEN	
	Every 12 hours	Every 8 hours
	200 mg/5 mL or 400 mg/5 mL oral suspension	125 mg/5 mL or 250 mg/5 mL oral suspension
Otitis media, sinusitis, lower respiratory tract infections, and more severe infections	45 mg/kg/day every 12 hours	40 mg/kg/day every 8 hours
Less severe infections	25 mg/kg/day every 12 hours	20 mg/kg/day every 8 hours

Patients Weighing 40 kg or More: Pediatric patients weighing 40 kg or more should be dosed according to adult recommendations.

Patients with Renal Impairment

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

Directions for Mixing Oral Suspension

Prepare a suspension at time of dispensing as follows: Tap bottle until all the powder flows freely. Add approximately 2/3 of the total amount of water for reconstitution and shake vigorously to suspend powder. Add remainder of the water and again shake vigorously.

Note: Shake oral suspension well before using. Reconstituted suspension must be stored under refrigeration and discarded after 10 days.

CONTRAINDICATIONS

Serious Hypersensitivity Reactions

Co-Amoxiclav is contraindicated in patients with a history of serious hypersensitivity reactions (e.g., anaphylaxis or Stevens-Johnson syndrome) to amoxicillin, clavulanate or to other beta-lactam antibacterial drugs (e.g., penicillin and cephalosporins).

Cholestatic Jaundice/Hepatic Dysfunction

Co-Amoxiclav is contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with Co-Amoxiclav

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam antibacterials, including Co-Amoxiclav These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. Before initiating therapy with Co-Amoxiclav careful inquiry should be made regarding previous hypersensitivity reactions to penicillin, cephalosporins, or other allergens. If an allergic reaction occurs, Co-Amoxiclav should be discontinued and appropriate therapy instituted.

Hepatic Dysfunction

Hepatic dysfunction, including hepatitis and cholestatic jaundice has been associated with the use of Co-Amoxiclav. Hepatic toxicity is usually reversible; however, deaths have been reported. Hepatic function should be monitored at regular intervals in patients with hepatic impairment.

Clostridium difficile Associated Diarrhea (CDAD)

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Co-Amoxiclav, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Skin Rash in Patients with Mononucleosis

A high percentage of patients with mononucleosis who receive amoxicillin develop an erythematous skin rash. Thus, Co-Amoxiclav should not be administered to patients with mononucleosis.

Potential for Microbial Overgrowth

The possibility of superinfections with fungal or bacterial pathogens should be considered during therapy. If superinfection occurs, amoxicillin/clavulanate potassium should be discontinued and appropriate therapy instituted.

Development of Drug-Resistant Bacteria

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

DRUG INTERACTIONS

Probenecid

Probenecid decreases the renal tubular secretion of amoxicillin but does not delay renal excretion of clavulanic acid. Concurrent use with Co-Amoxiclav result in increased and prolonged blood concentrations of amoxicillin. Coadministration of probenecid is not recommended.

Oral Anticoagulants

Abnormal prolongation of prothrombin time (increased international normalized ratio [INR]) has been reported in patients receiving amoxicillin and oral anticoagulants. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently with Co-Amoxiclav. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

Allopurinol

The concurrent administration of allopurinol and amoxicillin increases the incidence of rashes in patients receiving both drugs as compared to patients receiving amoxicillin alone. It is not known whether this potentiation of amoxicillin rashes is due to allopurinol or the hyperuricemia present in these patients.

Oral Contraceptives

Co-Amoxiclav may affect intestinal flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral estrogen/progesterone contraceptives.

Effects on Laboratory Tests

High urine concentrations of amoxicillin 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 Co-Amoxiclav, it is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.

Following administration of amoxicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone, and estradiol has been noted.

ADVERSE DRUG REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Anaphylactic reactions
- Hepatic Dysfunction
- CDAD

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most frequently reported adverse reactions were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%). Less than 3% of patients discontinued therapy because of drug-related adverse reactions. The overall incidence of adverse reactions, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported adverse reactions (<1%) include: Abdominal discomfort, flatulence, and headache.

In pediatric patients (aged 2 months to 12 years), 1 US/Canadian clinical trial was conducted which compared 45/6.4 mg/kg/day (divided every 12 hours) of CO-AMOXICLAV for 10 days versus 40/10 mg/kg/day (divided every 8 hours) of Co-Amoxiclav for 10 days in the treatment of acute otitis media. A total of 575 patients were enrolled, and only the suspension formulations were used in this trial. Overall, the adverse reactions seen were comparable to that noted above; however, there were differences in the rates of diarrhea, skin rashes/urticaria, and diaper area rashes.

Post marketing Experience

In addition to adverse reactions reported from clinical trials, the following have been identified during post marketing use of Co-Amoxiclav. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to Co-Amoxiclav

Gastrointestinal: Indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, mucocutaneous candidiasis, enterocolitis, and hemorrhagic/pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment.

Hypersensitivity Reactions: Pruritus, angioedema, serum sickness–like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia, and frequently fever), erythema multiforme, Stevens-Johnson syndrome, acute generalized exanthematouspustulosis, hypersensitivity vasculitis, and cases of exfoliative dermatitis (including toxic epidermal necrolysis) have been reported.

Liver: Hepatic dysfunction, including hepatitis and cholestatic jaundice, increases in serum transaminases (AST and/or ALT), serum bilirubin, and/or alkaline phosphatase, has been reported with Co-Amoxiclav. It has been reported more commonly in the elderly, in males, or in patients on prolonged treatment. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible. Deaths have been reported.

Renal: Interstitial nephritis, hematuria, and crystalluria have been reported.

Hemic and Lymphatic Systems: Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. Thrombocytosis was noted in less than 1% of the patients treated with Co-Amoxiclav. There have been reports of increased prothrombin time in patients receiving Co-Amoxiclav and anticoagulant therapy concomitantly.

Central Nervous System: Agitation, anxiety, behavioral changes, confusion, convulsions, dizziness, insomnia, and reversible hyperactivity have been reported.

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category B. Reproduction studies performed in pregnant rats and mice given Co-Amoxiclav (2:1 ratio formulation of amoxicillin: clavulanate) at oral doses up to 1200 mg/kg/day revealed no evidence of harm to the fetus due to Co-Amoxiclav The amoxicillin doses in rats and mice (based on body surface area) were approximately 4 and 2 times the maximum recommended adult human oral dose (875 mg every 12 hours). For clavulanate, these dose multiples were approximately 9 and 4 times the maximum recommended adult human oral dose (125 mg every 8 hours). 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. It is not known whether use of amoxicillin/clavulanate potassium in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood of the necessity for an obstetrical intervention.

Nursing Mothers

Amoxicillin has been shown to be excreted in human milk. Amoxicillin/clavulanate potassium use by nursing mothers may lead to sensitization of infants. Caution should be exercised when amoxicillin/clavulanate potassium is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of Co-Amoxiclav Powder for Oral Suspension have been established in pediatric patients. Use of Co-Amoxiclav in pediatric patients is supported by evidence from studies of Co-Amoxiclav in adults with additional data from a study of Co-Amoxiclav Powder for Oral Suspension in pediatric patients aged 2 months to 12 years with acute otitis media.

Because of incompletely developed renal function in neonates and young infants, the elimination of amoxicillin may be delayed; clavulanate elimination is unaltered in this age group. Dosing of Co-Amoxiclav should be modified in pediatric patients aged <12 weeks (<3 months).

Geriatric Use

Of the 3,119 patients in an analysis of clinical studies of Co-Amoxiclav, 32% were ≥65 years old, and 14% were ≥75 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and 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.

This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug 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.

Dosing in Renal Impairment

Amoxicillin is primarily eliminated by the kidney and dosage adjustment is usually required in patients with severe renal impairment (GFR <30 mL/min). See Patients with Renal Impairment (2.3) for specific recommendations in patients with renal impairment.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at pv@searlecompany.com

OVERDOSE

In case of overdosage, discontinue medication, treat symptomatically, and institute supportive measures as required. 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 symptoms1.

Interstitial nephritis resulting in oliguric renal failure has been reported in patients after overdosage with amoxicillin/clavulanate potassium.

Crystalluria, in some cases leading to renal failure, has also been reported after amoxicillin/clavulanate potassium overdosage in adult and pediatric patients. In case of overdosage, adequate fluid intake and diuresis should be maintained to reduce the risk of amoxicillin/clavulanate potassium crystalluria.

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/clavulanate potassium. Amoxicillin/clavulanate potassium may be removed from circulation by hemodialysis.

PHARMACOLOGICAL PROPERTIES

Mechanism of Action

CO-AMOXICLAV is an antibacterial drug.

Pharmacokinetics

Mean amoxicillin and clavulanate potassium pharmacokinetic parameters in normal adults following administration of Co-Amoxiclav Tablets are shown in Table 3 and following administration of Co-Amoxiclav Powder for Oral Suspension are shown below.

Table 3: Mean (±S.D.) Amoxicillin and Clavulanate Potassium Pharmacokinetic Parametersa,b with Co-Amoxiclav Tablets

Dose and Regimen	Cmax (mcg/mL)		AUC0-24 (mcg*h/mL)	
Amoxicillin/Clavulanate potassium	Amoxicillin	Clavulanate potassium	Amoxicillin	Clavulanate potassium
250/125 mg every 8 hours	3.3 ± 1.12	1.5 ± 0.70	26.7 ± 4.56	12.6 ± 3.25
500/125 mg every 12 hours	6.5 ± 1.41	1.8 ± 0.61	33.4 ± 6.76	8.6 ± 1.95
500 125 mg every 8 hours	7.2 ± 2.26	2.4 ± 0.83	53.4 ± 8.87	15.7 ± 3.86
875/125 mg every 12 hours	11.6 ± 2.78	2.2 ± 0.99	53.5 ± 12.31	10.2 ± 3.04

a Mean (± standard deviation) values of 14 normal adults (N=15 for clavulanate potassium in the low-dose regimens). Peak concentrations occurred approximately 1.5 hours after the dose.

b Amoxicillin/clavulanate potassium administered at the start of a light meal.

Mean (±S.D.) Amoxicillin and Clavulanate Potassium Pharmacokinetic Parameters a,b with Co-Amoxiclav **Powder for Oral Suspension**

Oral administration of 5 mL of 250 mg/5 mL suspension of Co-Amoxiclav or the equivalent dose of 10 mL of 125 mg/5 mL suspension of Co-Amoxiclav provides average peak serum concentrations approximately 1 hour after dosing of 6.9 mcg/mL for amoxicillin and 1.6 mcg/mL for clavulanic acid. The areas under the serum concentration curves obtained during the first 4 hours after dosing were 12.6 mcg*h/mL for amoxicillin and 2.9 mcg*h/mL for clavulanic acid when 5 mL of 250 mg/5 mL suspension of Co-Amoxiclav or equivalent dose of 10 mL of 125 mg/5 mL suspension of Co-Amoxiclav were administered to normal adults.

Amoxicillin serum concentrations achieved with Co-Amoxiclav are similar to those produced by the oral administration of equivalent doses of amoxicillin alone. Time above the minimum inhibitory concentration of 1 mcg/mL for amoxicillin has been shown to be similar after corresponding every 12 hour and every 8 hour dosing regimens of Co-Amoxiclav in adults and children.

Absorption: Dosing in the fasted or fed state has minimal effect on the pharmacokinetics of amoxicillin. While Co-Amoxiclav can be given without regard to meals, absorption of clavulanate potassium when taken with food is greater relative to the fasted state. In one study, the relative bioavailability of clavulanate was reduced when Co-Amoxiclav was dosed at 30 and 150 minutes after the start of a high-fat breakfast.

Distribution: Neither component in Co-Amoxiclav is highly protein-bound; clavulanic acid is approximately 25% bound to human serum and amoxicillin approximately 18% bound.

Amoxicillin diffuses readily into most body tissues and fluids with the exception of the brain and spinal fluid.

Two hours after oral administration of a single 35 mg/kg dose of suspension of Co-Amoxiclav to fasting children, average concentrations of 3 mcg/mL of amoxicillin and 0.5 mcg/mL of clavulanic acid were detected in middle ear effusions.

Metabolism and Excretion: The half-life of amoxicillin after the oral administration of Co-Amoxiclav is 1.3 hours and that of clavulanic acid is 1 hour.

Approximately 50% to 70% of the amoxicillin and approximately 25% to 40% of the clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of a single 250-mg or 500-mg tablet of Co-Amoxiclav

Microbiology

Amoxicillin is a semisynthetic antibiotic with in vitro bactericidal activity against Gram-positive and Gram-negative bacteria. Amoxicillin is, however, susceptible to degradation by beta-lactamases, and therefore, the spectrum of activity does not include organisms which produce these enzymes. Clavulanic acid is a beta-lactam, structurally related to the penicillin, which possesses the ability to inactivate some beta-lactamase enzymes commonly found in microorganisms resistant to penicillin and cephalosporins. In particular, it has good activity against the clinically important plasmid-mediated beta-lactamases frequently responsible for transferred drug resistance.

The formulation of amoxicillin and clavulanic acid in Co-Amoxiclav protects amoxicillin from degradation by some beta-lactamase enzymes and extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin.

Amoxicillin/clavulanic acid has been shown to be active against most isolates of the following bacteria, both in vitro and in clinical infections as described in the INDICATIONS AND USAGE section**.**

Table 4: Gram-positive bacteria

Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion (zone diameters in mm)					
Pathogen	S	I	R	S	I	R
Enterobacteriaceae	8/4	16/8	32/16	>18	14-17	≥13
Haemophilus influenzae and Staphylococcus aureus	4/2	--	8/4	>20	--	≤19

Staphylococcus aureus

Gram-negative bacteria

Enterobacter species

Escherichia coli

Haemophilus influenzae

Klebsiella species

Moraxella catarrhalis

The following in vitro data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for amoxicillin/clavulanic acid. However, the efficacy of amoxicillin/clavulanic acid in treating clinical infections due to these bacteria has not been established in adequate and well-controlled clinical trials.

Gram-positive bacteria

Enterococcus faecalis

Staphylococcus epidermidis

Staphylococcus saprophyticus

Streptococcus pneumoniae

Streptococcus pyogenes

Viridans group Streptococcus

Gram-negative Bacteria

Eikenellacorrodens

Proteus mirabilis

Anaerobic Bacteria

Bacteroidesspecies including *Bacteroides fragilis*

Fusobacterium species

Peptostreptococcus species

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide the results of in vitro susceptibility test results for antimicrobial drug products used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

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 test method2,3 (broth and/or agar). The MIC values should be interpreted according to criteria provided in Table 5.

Diffusion techniques:

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method3,4. This procedure uses paper disks impregnated with 30 mcg amoxicillin/clavulanic acid (20 mcg amoxicillin plus 10 mcg clavulanic acid) to test the susceptibility of bacteria to amoxicillin/clavulanic acid. The disc diffusion interpretive criteria are provided in Table 5.

Table 5: Susceptibility Test Interpretive Criteria for Amoxicillin Clavulanic Acid

Quality Control:

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test2,3,4. Standard amoxicillin/clavulanic acid powder should provide the following range of MIC values noted in Table 6 for the diffusion technique using the 30 mcg amoxicillin/clavulanic acid (20 mcg amoxicillin plus 10 mcg clavulanic acid) disk, the criteria in Table 6 should be achieved.

Table 6: Acceptable Quality Control Ranges for Amoxicillin/Clavulanic Acid

QC Strain	Minimum Inhibitory Concentration (mcg/mL)	Disk Diffusion(zone diameter in mm)
Escherichia coli ATCC 25922	2/1 to 8/4	18 to 24
Escherichia coli ATCC 35218	4/2 to 16/8	17 to 22
Haemophilus influenzae ATCC 49247	2/1 to 16/8	15 to 23
Staphylococcus aureus ATCC 29213	0.12/0.06 to 0.5/0.25	--
Staphylococcus aureus ATCC 29523	--	28 to 36

Summary of Clinical studies

CLINICAL STUDIES

Lower Respiratory Tract and Complicated Urinary Tract Infections

Data from 2 pivotal trials in 1,191 patients treated for either lower respiratory tract infections or complicated urinary tract infections compared a regimen of 875-mg tablets of Co-Amoxiclav every 12 hours to 500-mg tablets of Co-Amoxiclav dosed every 8 hours (584 and 607 patients, respectively). Comparable efficacy was demonstrated between the every 12 hours and every 8 hours dosing regimens. There was no significant difference in the percentage of adverse events in each group. The most frequently reported adverse event was diarrhea; incidence rates were similar for the 875-mg every 12 hours and 500-mg every 8 hours dosing regimens (15% and 14%, respectively); however, there was a statistically significant difference ($p < 0.05$) in rates of severe diarrhea or withdrawals with diarrhea between the regimens: 1% for 875-mg every 12 hours regimen versus 2% for the 500-mg every 8 hours regimen.

In one of these pivotal trials, patients with either pyelonephritis (n = 361) or a complicated urinary tract infection (i.e., patients with abnormalities of the urinary tract that predispose to relapse of bacteriuria following eradication, n = 268) were randomized (1:1) to receive either 875-mg tablets of Co-Amoxiclav every 12 hours (n=308) or 500-mg tablets of Co-Amoxiclav every 8 hours (n=321).

The number of bacteriologically evaluable patients was comparable between the two dosing regimens. Co-Amoxiclav produced comparable bacteriological success rates in patients assessed 2 to 4 days immediately following end of therapy. The bacteriologic efficacy rates were comparable at one of the follow-up visits (5 to 9 days post-therapy) and at a late post-therapy visit (in the majority of cases, this was 2 to 4 weeks post-therapy), as seen in Table 7.

Table 7: Bacteriologic efficacy rates for Co-Amoxiclav

Time Post Therapy	875 mg every 12 hours% (n)	500 mg every 8 hours% (n)
2 to 4 days	81% (58)	80% (54)
5 to 9 days	58% (41)	52% (52)
2 to 4 weeks	52% (101)	55% (104)

As noted before, though there was no significant difference in the percentage of adverse events in each group, there was a statistically significant difference in rates of severe diarrhea or withdrawals with diarrhea between the regimens.

Acute Bacterial Otitis Media and Diarrhea in Pediatric Patients

One US/Canadian clinical trial was conducted which compared 45/6.4 mg/kg/day (divided every 12 hours) of Co-Amoxiclav for 10 days versus 40/10 mg/kg/day (divided every 8 hours) of Co-Amoxiclav for 10 days in the treatment of acute otitis media. Only the suspension formulations were used in this trial. A total of 575 pediatric patients (aged 2 months to 12 years) were enrolled, with an even distribution among the 2 treatment groups and a comparable number of patients were evaluable (i.e., ³ 84%) per treatment group. Otitis media-specific criteria were required for eligibility and a strong correlation was found at the end of therapy and follow-up between these criteria and physician assessment of clinical response. The clinical efficacy rates at the end of therapy visit (defined as 2-4 days after the completion of therapy) and at the follow-up visit (defined as 22-28 days post-completion of therapy) were comparable for the 2 treatment groups, with the following cure rates obtained for the evaluable patients: At end of therapy, 87% (n = 265) and 82% (n = 260) for 45 mg/kg/day every 12 hours and 40 mg/kg/day every 8 hours, respectively. At follow-up, 67% (n = 249) and 69% (n = 243) for 45 mg/kg/day every 12 hours and 40 mg/kg/day every 8 hours, respectively.

Diarrhea was defined as either: (a) 3 or more watery or 4 or more loose/watery stools in 1 day; OR (b) 2 watery stools per day or 3 loose/watery stools per day for 2 consecutive days. The incidence of diarrhea was significantly lower in patients who received the every 12 hours regimen compared to patients who received the every 8 hours regimen (14% and 34%, respectively). In addition, the number of patients with either severe diarrhea or who were withdrawn with diarrhea was significantly lower in the every 12 hours treatment group (3% and 8% for the every 12 hours/10 day

and every 8 hours/10 day, respectively). In the every 12 hours treatment group, 3 patients (1%) were withdrawn with an allergic reaction, while 1 patient in the every 8 hours group was withdrawn for this reason. The number of patients with a candidal infection of the diaper area was 4% and 6% for the every 12 hours and every 8 hours groups, respectively.

It is not known if the finding of a statistically significant reduction in diarrhea with the oral suspensions dosed every 12 hours, versus suspensions dosed every 8 hours.

PRECLINICAL SAFETY DATA

Carcinogenesis, Mutagenesis, Impairment Of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Co-Amoxiclav (4:1 ratio formulation of amoxicillin: clavulanate) was non-mutagenic in the Ames bacterial mutation assay, and the yeast gene conversion assay. Co-Amoxiclav 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. Co-Amoxiclav 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.

Co-Amoxiclav (2:1 ratio formulation of amoxicillin: clavulanate) at oral doses of up to 1,200 mg/kg/day was found to have no effect on fertility and reproductive performance in rats. Based on body surface area, this dose of amoxicillin is approximately 4 times the maximum recommended adult human oral dose (875 mg every 12 hours). For clavulanate, the dose multiple is approximately 9 times higher than the maximum recommended adult human oral dose (125 mg every 8 hours), also based on body surface area.

PRESENTATION

Fortecin 375 mg tablets are available as a bottle of 6 TABLET USP
Fortecin 625mg tablets are available as a bottle of 6 TABLET USP
Fortecin BD 1g tablets are available as a bottle of 6 TABLET USP
Fortecin 156.25mg/5ml suspension Powder is available as a bottle of 60 ml suspension USP
Fortecin DS 312.5mg/5ml suspension Powder are available as a bottle of 60 ml suspension USP

INSTRUCTIONS

- To be sold on the prescription of a registered medical practitioner only.
- Store below 30°C.
- Protect from sunlight and heat.
- Keep all medicines out of sight and reach of children.
- Do not freeze.

REGISTRATION NUMBER

Fortecin 375 mg tablet Reg.NO.015977
Fortecin 625mg tablet Reg.NO.017296
Fortecin BD 1g tablet Reg.NO.023032
Fortecin 156.25mg/5ml suspension Reg.NO.015978
Fortecin DS 312.5mg/5ml suspension Reg.NO.015978

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Manufactured by:

ICI PAKISTAN Ltd.

Pharmaceuticals

32/2A, Phase lll, Industrial Estate

Hattar-Pakistan

Marketed by:

The Searle Company Limited,

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