Overdosage:
In case of overdose patients should be treated symptomatically and supportive measures should be applied. If the drug has been ingested only recently emesis should be induced or gastric lavage should be performed. In patients with kidney disease very high plasma concentrations may be established rapidly. Both amoxicillin and Clavulanic acid can be removed from the blood by hemodialysis. There is no known antidote for neither amoxicillin nor Clavulanic acid. In a clinical study involving 51 pediatric patients, it has been reported that overdoses less than 250 mg/kg of amoxicillin are not associated with clinically important symptoms and do not require gastric evacuation.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties:
Clavulanic acid binds and inhibits beta-lactamases that inactivate amoxicillin resulting in amoxicillin having an expanded spectrum of activity. Amoxicillin inhibits bacterial cell wall synthesis by binding to one or more of the penicillin binding proteins (PBPs); which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Bacteriology: Amoxicillin/Clavulanic acid is active in vitro and in clinical infections (see INDICATIONS section) against most strains of the following bacteria which may or may not be beta-lactamase producers.
GRAM-POSITIVE AEROBES: Staphylococcus aureus (methicillin/oxacillin resistant staphylococci are considered also to be resistant to amoxicillin/ clavulanic acid). Staphylococcus epidermidis, Staphylococcus saprophyticus, Streptococcus pneumoniae, Streptococcus pyogenes, Viridans group streptococci, Enterococcus faecalis, Listeria monocytogenes, Bacillus anthracis, Corynebacterium species.
GRAM-NEGATIVE AEROBES: Enterobacter spp., Escherichia coli, Haemophilus infl uenzae, Klebsiella spp., Moraxella catarrhalis, Eikenella corrodens, Neisseria gonorhoeae, Proteus mirabilis, Pasteurella multocida, Neisseria meningitides, Salmonella spp., Shigella spp., Bordetella pertussis, Brucella species, Vibrio cholerae.
ANAEROBIC BACTERIA: Bacteroides spp., Bacteroides fragilis, Fusobacterium spp., Peptostreptococcus spp., Clostridia species, Peptococcus species.

Pharmacokinetic properties:
Following oral administration of **DAFRACLAV®**, the bioavailability of Amoxicillin is between 72-94% and that of Clavulanic acid is 75%. Fasting or fed conditions affect minimally the bioavailability for Amoxicillin and Clavulanic acid. Both substances distribute into the most body tissues and fluids. However, under normal conditions, the passage into cerebrospinal fluid is insignificant. Binding to plasma proteins is 18% for Amoxicillin and 25% Clavulanic acid. Both substances are partially metabolized into the liver, and 50-72% amoxicillin and 25-40% Clavulanic acid are excreted unchanged into the urine in 6 hours. The half-life is 1.3 hours for Amoxicillin and 1 hour for Clavulanic acid.

DAFRA PHARMA INTERNATIONAL
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3FIDCLAVE 2021

Dafraclav®

amoxicillin & clavulanic acid

EUROPEAN GMP

The winning combination of amoxicillin, clavulanic acid and the Dafra quality

Suitable dosage:
1 pack = 1 basic treatment of seven days

First-choice antibiotic for ENT, respiratory tract and skin infections

Dafra PHARMA

Setting the Standard

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Dafraclav®

QUALITATIVE AND QUANTITATIVE COMPOSITION:
DAFRACLAV® 625 mg Filmcoated tablet (15 tablets); **DAFRACLAV®** 1 g Filmcoated tablet (15 tablets);
Dry powder **DAFRACLAV®** BD 400/57 mg Forte Oral Suspension, 70 ml;
Dry powder **DAFRACLAV®** BD 200/28 mg Pediatric Oral Suspension, 70 ml.

Posology and method of administration:
DAFRACLAV® must be taken before or during meals.
The absorption of Clavulanic acid is better when **DAFRACLAV®** is taken before the meal.
DAFRACLAV® 1000 mg is not indicated for patients on haemodialysis.

INDICATIONS AND DOSAGE

INDICATIONS	SEVERITY	TABLETS	SUSPENSION (From 3 months)
Upper respiratory tract infections	Less severe / moderate	625 mg 3 x / day	12,5 mg/kg 2 x / day
	severe	1000 mg 2 x / day	22,5 mg/kg 2 x / day
Lower respiratory tract infections	Less severe / moderate	625 mg 3 x / day	12,5 mg/kg 2 x / day
	severe	1000 mg 2 x / day	22,5 mg/kg 2 x / day
Soft tissue and skin infections	Less severe / moderate	625 mg 3 x / day	12,5 mg/kg 2 x / day
	severe	1000 mg 2 x / day	22,5 mg/kg 2 x / day
Urinary tract infections	Less severe / moderate	625 mg 3 x / day	12,5 mg/kg 2 x / day
	severe	1000 mg 2 x / day	22,5 mg/kg 2 x / day

Renal impairment: dosage adjustment if
the glomerular filtration rate <30 ml / min.

ADVANTAGES AND KEY POINTS

- **DAFRACLAV®** is a combination of amoxicillin and clavulanic acid, having an expanded spectrum of activity. It has bactericidal properties against most gram-positive and gram-negative strains, including anaerobic bacteria*.
- **DAFRACLAV®** is at your disposal:
  - In four dosages for oral administration: tablets of 625mg and 1g; powder for oral suspension (200/28mg and 400/56mg).
  - In packs with an optimal number of tablets in function of the dosage, avoiding spillage.
- **DAFRACLAV®** is the winning combination of amoxicillin and clavulanic acid with the quality from Dafra:manufactured in Europe according to European GMP and at an affordable price.

(*) Prescribing information Dafraclav, Dafra Pharma (2008)

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PRESCRIBING INFORMATION

Contraindications:
DAFRACLAV® is contraindicated in patients with a history of penicillin allergy. It is also contraindicated in patients with a history of cholestatic jaundice or hepatic dysfunction resulting from the use of amoxicillin/Clavulanic acid.

Special warnings and precautions for use:
During penicillin therapy serious hypersensitivity (anaphylactic) reactions may occur. These reactions are more likely to appear in persons with a history of hypersensitivity to penicillin or multiple allergens. Prior to the initiation of **DAFRACLAV®** therapy. Careful inquiry should be made concerning previous hypersensitivity reactions to penicillin, cephalosporins and other allergens. If allergic reactions occur during therapy, treatment should be discontinued immediately.
In serious anaphylactic reactions administration of adrenaline, oxygen, intravenous steroids and intubation may be necessary. Pseudomembranous colitis has been reported in association with all antibiotics including amoxicillin/Clavulanic acid. This possibility should be taken into consideration in patients presenting with diarrhea. **DAFRACLAV®** should be used carefully in patients with renal or hepatic dysfunction. During prolonged therapy hepatic, renal and hematopoetic functions should be assessed periodically. Administration of ampicillin to infectious mononucleosis patients has been reported to be associated with a morbilliform erythema. **DAFRACLAV®** should not be used in these patients. If bacterial or mycotic superinfections occur during therapy (usually Pseudomonas or Candida) treatment should be discontinued and appropriate treatment should be instituted.

Interactions with other medicinal products:
Drug Interactions: Probenecid inhibits renal tubular secretion of amoxicillin and elevates its plasma concentrations. **DAFRACLAV®** should not be used simultaneously with probenecid. Concurrent use of ampicillin with allopurinol increases the incidence of skin rashes. It is not known whether this is due to allopurinol or hyperuricemia. **DAFRACLAV®** should not be used in conjunction with disulfiram.
Diagnostic test interactions: Amoxicillin passes into urine in high concentrations and may cause the tests used for the demonstration of glucose in the urine to give false positive results. When testing for the presence of glucose in the urine it is recommended that tests based on enzymatic glucose oxidase method be used. Administration of amoxicillin to pregnant women results in the elevation of total conjugated estriol, estriol glucuronides, conjugated estrone and estradiol levels in serum.

Pregnancy and lactation:
Pregnancy Category B: although animal experiments did not demonstrate any teratogenic potential for amoxicillin/clavulanic acid, controlled studies in humans have not been carried out. **DAFRACLAV®** should be used in pregnancy only if it is clearly needed. Antibiotics of ampicillin class diffuse into human milk. **DAFRACLAV®** should be used carefully in nursing mothers.

Effects on ability to drive and use other machines:
DAFRACLAV® has no pharmacodynamic action that can interfere with driving or machine operating skills.

Undesirable effects:
Amoxicillin/Clavulanic acid combination is generally well tolerated. In clinical trials most of the reported side-effects are light and transient in nature. Less than 3% of patients discontinued treatment because of side effects. Diarrhea (9%), nausea (3%), skin rash and urticaria (3%), vomiting (1%) and vaginitis (1%) have been reported most frequently. At high dose levels the incidence of side effects is higher. Abdominal discomfort, flatulence and headache have been reported less frequently. The following side-effects have been reported with ampicillin class of antibiotics:
Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black hairy tongue, mucocutanous candidiasis, enterocolitis and hemorrhage, pseudomembraneous colitis. Hypersensitivity reactions: Skin rash, pruritus, urticaria, angioedema, serum sickness-like reaction and rarely exfoliative dermatitis. These reactions can be controlled by the administration of antihistaminics and if necessary, corticosteroids. Liver: Increases in AST(SGOT) and ALT (SGPT) values have been observed during therapy. Less frequently, in addition to these changes, elevation of bilirubin and alkaline phosphatase values and cholestatic and hepatocellular changes in biopsies have been reported. These changes, in general, are reversible. Renal: Interstitial nephritis and hematuria have been reported rarely. Hematopoetic-Lymphatic system: During therapy with penicillins anemia, hemolytic anemia, thrombocytopenia, eosinophilia, leucopenia and agranulocytosis have been reported. These reactions are generally reversible and disappear on discontinuing the treatment. Central nervous system: Agitation, anxiety, confusion, hyperactivity have been reported infrequently.

For the complete SMPC, please visit www.dafrapharma.com