PACKAGE INSERT FOR AMOCLAN & AMOCLAN FORTE

Scheduling Status: S4

Proprietary names and dosage form:

AMOCLAN Tablets

AMOCLAN FORTE Tablets

Composition:

Each AMOCLAN tablet contains: amoxycillin trihydrate equivalent to amoxycillin 250 mg and potassium clavulanate equivalent to 125 mg clavulanic acid.

Each AMOCLAN FORTE tablet contains: amoxycillin trihydrate equivalent to amoxycillin 500 mg and potassium clavulanate equivalent to 125 mg clavulanic acid.

Sugar free

Pharmacological classification:

A 20.1.2 Penicillins

Pharmacological actions:

AMOCLAN and **AMOCLAN FORTE** is combination of amoxycillin and clavulanic acid.

Amoxycillin is a semisynthetic beta-lactamase-susceptible penicillin, which has *in vitro* bactericidal activity against a broad spectrum of non-lactamase-producing Gram positive and Gram negative organisms. The spectrum of activity does not include those organisms that produce beta-lactamases, namely resistant staphylococci, and all strains of *Pseudomonas, Klebsiella and Enterobacter.*

Clavulanic acid has been shown in vitro to be an irreversible inhibitor of beta-lactamases produced by: *Staphylococcus aureus*, *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Proteus vulgaris, Haemophilus influenzae, Neisseria gonorrhoea and Bacteroides fragilis.*
Clavulanic acid does not inactivate the chromosomally mediated (Sykes Type 1 Cephalosporinase) beta-lactamases produced by *Acinetobacter* species, *Citrobacter* species, *Entrobacter*, Indole positive *Proteus, Providencia* species and *Serratia marcescens*. In vitro the formulation showed synergism against amoxycillin-resistant organisms, with no evidence of antagonism, and the activity was not reduced in the presence of serum. (In vitro activity does not necessarily imply *in vivo* efficacy). The clavulanic acid component has very little bactericidal action.

Pharmacokinetics:

Absorption:

Amoxycillin is stable in the presence of acidic gastric secretions. Peak blood levels are achieved 1 to 2 hours after administration. There is a linear dose response in peak serum levels. The pharmacokinetics of amoxycillin and clavulanic acid are closely allied and neither is adversely effected by the presence of food in the stomach.

Distribution:

Approximately 18 % of the total plasma amoxycillin content is protein bound. Amoxycillin diffuses readily into most body tissues with the exception of the brain and spinal fluid. Inflammation generally increases the permeability of the meninges to penicillins and this may apply to amoxycillin.

Excretion:

The elimination half-life of amoxycillin is approximately 1 hour. Co-administration of probenecid has little effect on the excretion of the clavulanic acid component of the formulation. Small amounts of amoxycillin are also excreted in the faeces and bile.

Indications:

AMOCLAN and **AMOCLAN FORTE** formulations are indicated for the treatment of infections caused by amoxycillin resistant organisms producing beta-lactamases sensitive to clavulanic acid:

- Upper respiratory tract infections such as sinusitis, recurrent otitis media and tonsillitis.
- Lower respiratory tract infections such as bronchitis and bronchopneumonia.
- Genito-urinary tract infection such as cystitis, urethritis and pyelonephritis.
- Skin and soft tissue infections.

AMOCLAN and **AMOCLAN FORTE** formulations will also be effective in the treatment of infections caused by amoxycillin sensitive organisms at appropriate amoxycillin dosage, since in this situation the clavulanic acid component does not contribute to the therapeutic effect.

Contra-indications:

Hypersensitivity to penicillins or to cephalosporins. Cross-sensitivity between penicillins and cephalosporins is well documented.
AMOCLAN and **AMOCLAN FORTE** are contra-indicated in patients with a previous history of amoxycillin/clavulanic acid-associated jaundice or hepatic dysfunction.

Warnings:

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. Before initiating therapy with **AMOCLAN** and **AMOCLAN FORTE**, careful enquiry should be made concerning previous hypersensitivity reactions to penicillin, cephalosporins or other allergens.

Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity, who have experienced severe reactions when treated with cephalosporins.

If an allergic reaction occurs **AMOCLAN** and **AMOCLAN FORTE** should be discontinued and appropriate therapy instituted. Serious anaphylactic reactions may require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids and airway management, including intubation may also be required.

AMOCLAN and **AMOCLAN FORTE** should be avoided if infectious mononucleosis is suspected, since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxycillin.

Prolonged use may result in overgrowth of non-susceptible organisms.
Pseudomembranous enterocolitis has been reported.

Prolongation of prothrombin time has been reported rarely in patients receiving **AMOCLAN** and **AMOCLAN FORTE**. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently.
Periodic assessment of organ function, including renal, hepatic and haematopoietic functions is advisable during prolonged therapy.

Transient hepatitis and cholestatic jaundice has been reported. **AMOCLAN** and **AMOCLAN FORTE** should be used with caution in patients with evidence of hepatic dysfunction.

Interactions:

Probenecid decreases the renal tubular secretion of amoxycillin, but does not effect clavulanic acid excretion. Concurrent use with **AMOCLAN** and **AMOCLAN FORTE** may result in increased and prolonged blood levels of amoxycillin but not of clavulanic acid.

AMOCLAN and **AMOCLAN FORTE** may reduce the efficacy of oral contraceptives and patients should be warned accordingly.

The concomitant administration of allopurinol and ampicillin substantially increases the incidence of skin rashes in patients receiving both agents, as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricaemia present in these patients.

Tetracyclines and other bacteriostatic drugs may interfere with the bactericidal effects of amoxycillin.
Interaction with laboratory test:

It is recommended that when testing for the presence of glucose in urine during **AMOCLAN** and **AMOCLAN FORTE** treatment, enzymatic glucose oxidase methods should be used. Due to the high urinary concentrations of amoxycillin, false positive readings are common with chemical methods.

Pregnancy and lactation:

Use in pregnancy:

The safety of **AMOCLAN** and **AMOCLAN FORTE** in pregnancy has not been established.

Use in lactation:

Amoxycillin is distributed into breast milk. Although significant problems in humans have not been documented, the use of amoxycillin by nursing mothers may lead to sensitisation, diarrhoea, candidiasis and skin rash in the infant.

Dosage and directions for use:

Tablets should be taken immediately before a meal**.**

Dosages:

General information: for infections caused by amoxycillin sensitive organisms the dosage is that approved for amoxicillin, as the clavulanic acid component does not contribute to the therapeutic effect.

Adults:

The adult dose for **AMOCLAN** is one **AMOCLAN** tablet every 8 hours at the start of a meal. For more severe infections and infection of the respiratory tract, the dose should be one **AMOCLAN FORTE** tablet every 8 hours at the start of a meal.

Since **AMOCLAN** and **AMOCLAN FORTE** tablets contain the same amount of clavulanic acid (125 mg as the potassium salt) two **AMOCLAN** tablets are not equivalent to one **AMOCLAN FORTE** tablet. Therefore two **AMOCLAN** tablets should not be substituted for one **AMOCLAN FORTE** tablet for the treatment of more severe infections.

Impaired renal function:

Both amoxycillin and clavulanic acid are excreted by the kidneys and the serum half-life of each increases in patients with renal failure. Therefore, the dose may need to be reduced or the interval extended. Dosage adjustments are based on the maximum recommended level of amoxycillin. The following schedule is proposed:

AMOCLAN and **AMOCLAN FORTE**:
Mild impairment (creatinine clearance greater than 30 ml/minute): no change in dosage
Moderate impairment (creatinine clearance 10 to 30 ml/minute): 1 tablet every 12 hours
Severe impairment (creatinine clearance less than 10 ml/minute): half a tablet every 12 hours.

Haemodialysis decreases serum concentrations of both amoxycillin and clavulanic acid and an additional dose should be administered at the end of dialysis.

Dosage guide:

Amoxycillin-sensitive organisms:

Product	Upper respiratory tract infections	Lower respiratory tract infections	Urinary tract infections	Skin and soft tissue infections
AMOCLAN	1 tablet 8 hourly	----------	1 tablet 8 hourly	1 tablet 8 hourly
AM OCLAN FORTE	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly

Amoxycillin-resistant organisms:

Product	Upper respiratory tract infections	Lower respiratory tract infections	Urinary tract infections	Skin and soft tissue infections
AMOCLAN	----------	----------	1 tablet 8 hourly	1 tablet 8 hourly
AMOCLAN FORTE	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly

Side-effects and special precautions:

The most frequently reported adverse effects are diarrhoea, nausea, vomiting, indigestion, abdominal pain, skin rashes, urticaria and erythema multiforme, vaginitis, abnormal taste, headache, dizziness, tiredness and hot flushes.

The incidence and severity of adverse effects, particularly nausea and diarrhoea, increased with the higher recommended dose and can be minimized by administering **AMOCLAN** and **AMOCLAN FORTE** at the start of a meal. In addition, as these symptoms are especially related to the potassium clavulanate component, where these gastro-intestinal symptoms occur and a higher concentration of amoxycillin is required, consideration should be given to administering the additional amoxycillin separately.

The following adverse reactions have been reported and may occur with **AMOCLAN** and **AMOCLAN FORTE**.

Hypersensitivity reactions:

Skin rashes, pruritus and urticaria, serum sickness-like syndrome, erythema multiforme, rare cases of Steven-Johnson syndrome, hypersensitivity vasculitis, and less frequently bullous exfoliative dermatitis and toxic epidermal necrolysis have been reported. Whenever such reactions occur, **AMOCLAN** and **AMOCLAN FORTE** should be discontinued. Serious and occasional fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema can occur with oral penicillin (see "**Warnings**").

Interstitial nephritis can occur rarely.

Gastro-intestinal reactions:

Nausea, vomiting, diarrhoea, gastritis, stomatitis, glossitis, black 'hairy' tongue, enterocolitis, mucocutaneous candidiasis and antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis). If gastro-intestinal reactions are evident, they may be reduced by taking **AMOCLAN** and **AMOCLAN FORTE** at the start of a meal.

Hepatic effects:

Hepatitis and cholestatic jaundice have been reported. The events may be severe and occur predominantly in adult or elderly patients. Signs and symptoms usually occur during or shortly after treatment, but in some cases may not become apparent until several weeks after treatment has ceased. **The hepatic effects are usually reversible. However, in extremely rare circumstances, death has been reported. These have almost always been cases associated with serious underlying diseases or concomitant medication.**

A moderate raise in aspartate transaminase (AST) and/or Alanine transaminase (ALT) has been noted in patients treated with **AMOCLAN** and **AMOCLAN FORTE**, but the significance of these findings is unknown.

Renal effects:

Crystalluria has been reported.

Haematological effects:

Haemolytic anaemia, reversible thrombocytopenia, thrombocytopenic purpura, eosinophilia, reversible leucopenia and agranulocytosis have been reported. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1 % of the patients treated with **AMOCLAN** and **AMOCLAN FORTE**. Prolongation of bleeding time and prothrombin time has also been reported less frequently. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly.

Central nervous system effects:

CNS effects have been seen rarely. These include reversible hyperactivity, dizziness, headache and convulsions. Convulsions may occur with impaired renal function or in those receiving high doses.

Miscellaneous:

Superficial tooth discolouration has been reported with the suspension and chewable tablet formulations. It can usually be removed by brushing.

Special precautions:

Caution is needed when administering amoxycillin to patients with syphilis, as the Jarisch-Herxheimer reaction may occur in these patients.

When high doses are administered, adequate fluid intake and urinary output must be maintained.

The sodium content must be taken into account in patients on a sodium-restricted diet if the administration of high doses is necessary.

The use of lignocaine or benzyl alcohol together with amoxycillin must be used only when administering an intramuscular injection and not given intravenously.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function, is advisable during prolonged therapy. Since **AMOCLAN** and **AMOCLAN FORTE** contains amoxycillin, an aminopenicillin, it is not the treatment of choice in patients presenting with sore throat or pharyngitis because of the possibility that the underlying cause is infectious mononucleosis, in the presence of which there is high incidence of rash if amoxycillin is used. **AMOCLAN** and **AMOCLAN FORTE** should be given with caution to patients with lymphatic leukemia since they are especially susceptible to amoxycillin-induced skin rashes.

The possibility of superinfections with mycotic or bacterial phathogens should be kept in mind during therapy. If superinfections do occur (usually involving *Aerobacter, Pseudomonas* or *Candida*), the agent should be discontinued and/or appropriate therapy instituted.

Impaired hepatic function:

Changes in liver function tests have been observed in some patients receiving **AMOCLAN** and **AMOCLAN FORTE**. It should be used with care in patients with evidence of severe hepatic dysfunction.

Impaired renal function:

In patients with moderate or severe renal impairment **AMOCLAN** and **AMOCLAN FORTE** dosage should be adjusted (See "**Dosage and administration**")

Use in lactation:

Amoxycillin is excreted in breast milk; there is no data on the excretion of clavulanic acid in human milk. Therefore caution should be exercised when **AMOCLAN** and **AMOCLAN FORTE** is administered to a nursing woman.

The use of **AMOCLAN** and **AMOCLAN FORTE** may lead to the selection of resistant strains of organisms and sensitivity testing should therefore be carried out whenever possible, to demonstrate the appropriateness of therapy.

Known symptoms of over dosage and particulars of its treatment:

Overdosage with amoxycillin is usually asymptomatic. However, gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and symptoms of water and electrolyte imbalance should be treated symptomatically.

Adequate fluid intake and urinary output must be maintained to minimise the possibility of crystalluria.

Amoxycillin may be removed from the circulation by haemodialysis. The molecular weight, degree of protein binding and pharmacokinetic profile of clavulanic acid, together with information from a single patient with renal insufficiency, all suggest that this compound may also be removed by haemodialysis.

Identification:

AMOCLAN: White to off-white film – coated scored tablets.

AMOCLAN FORTE: White to off-white film – coated large oval tablets.

Presentations:

AMOCLAN and **AMOCLAN FORTE**: 15 tablets in white plastic HDPE container.

Storage instructions:

Store at or below 25 ºC and protect from light and moisture.

Keep well closed.

KEEP OUT OF THE REACH OF CHILDREN.

Registration numbers:

AMOCLAN: 35/20.1.2/0232

AMOCLAN FORTE: 35/20.1.2/0233

Name and business address of the holder of the certificate of registration:

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