PACKAGE INSERT FOR MYCLAV 375 and 625

SCHEDULING STATUS

S4

PROPRIETARY NAME (AND DOSAGE FORM)

MYCLAV 375 (film coated tablet)

MYCLAV 625 (film coated tablet)

COMPOSITION

MYCLAV 375: Each film coated tablet contains amoxicillin trihydrate equivalent to 250,0 mg amoxicillin and clavulanate potassium Avicel (1:1) mixture equivalent to 125,0 mg clavulanic acid.

MYCLAV 625: Each film coated tablet contains amoxicillin trihydrate equivalent to 500,0 mg amoxicillin and clavulanate potassium Avicel (1:1) mixture equivalent to 125,0 mg clavulanic acid.

Inactive ingredients:

Magnesium stearate, sodium starch glycolate, colloidal anhydrous silica, microcrystalline cellulose, sodium lauryl sulphate, Opadry OY-C-7000A, methanol and dichloromethane.

PHARMACOLOGICAL CLASSIFICATION

A 20.1.2 Penicillins

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Bacteriology:

MYCLAV is a combination of amoxicillin and clavulanic acid.

Spectrum:

Amoxicillin is a semi-synthetic beta-lactamase-susceptible penicillin, which has *in vitro* bactericidal activity against a broad spectrum of non beta-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 gonorrhoeae* and *Bacteroides fragilis.*

Clavulanic acid does not inactivate the chromosomally-mediated (Sykes type 1 cephalosporinase) beta-lactamases produced by *Acinetobacter* species, *Citrobacter* species, *Enterobacter*, indole-positive *Proteus, Providencia* species and *Serratia marcescens*. *In vitro* the formulation showed synergism against amoxicillin-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.

Bactericidal action:

The amoxicillin component of the formulation exert a bactericidal action against many strains of Gram-positive and Gram-negative organisms. The clavulanic acid component has very little bactericidal action. It does however, by inactivation of susceptible beta-lactamases, protect amoxicillin from degradation by a large number of beta-lactamase enzymes produced by penicillin-resistant strains of organisms.

Pharmacokinetic properties

Absorption:

Amoxicillin is stable in the presence of acidic gastric secretions. Peak blood levels are achieved 1 – 2 hours after administration. There is a linear dose response in peak serum levels.

The pharmacokinetics of amoxicillin and clavulanic acid are closely allied and neither is adversely affected by the presence of food in the stomach.

Distribution:

Approximately 18 % of the total plasma amoxicillin content is protein bound. Amoxicillin 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 amoxicillin.

Excretion:

The elimination half-life of amoxicillin 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 amoxicillin are also excreted in the faeces and bile.

MYCLAV tablets are eliminated primarily unchanged through the renal route. Approximately 50 – 78 % of amoxicillin and 25 – 40 % of clavulanic acid are excreted unchanged in urine within the first 6 hours after administration.

INDICATIONS

MYCLAV is indicated for the treatment of infections caused by amoxicillin resistant organisms producing beta-lactamases, sensitive to clavulanic acid:

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

MYCLAV will also be effective in the treatment of infections caused by amoxicillin sensitive organisms at the appropriate amoxicillin dosage since in this situation the clavulanic acid component does not contribute to the therapeutic effect.

CONTRAINDICATIONS

Hypersensitivity to penicillins or to cephalosporins or to any of the other ingredients of **MYCLAV**. Cross-sensitivity between penicillins and cephalosporins is well documented.

MYCLAV is contraindicated in patients with a previous history of amoxicillin/clavulanic-associated jaundice/hepatic dysfunction.

WARNINGS AND SPECIAL PRECAUTIONS

- Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. Before initiating therapy with **MYCLAV**, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins, including **MYCLAV**. 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, which have experienced severe reactions when treated with cephalosporins.
- If an allergic reaction occurs, **MYCLAV** should be discontinued and the 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.
- **MYCLAV** 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 amoxicillin.
- Prolonged use may result in overgrowth of non-susceptible organisms. Pseudomembranous enterocolitis has been reported.
- Prolongation of prothrombin time has been reported in patients receiving **MYCLAV**. 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 have been reported. **MYCLAV** should be used with caution in patients with evidence of hepatic dysfunction.

Special precautions:

- Caution is needed when administering **MYCLAV** 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.
- Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function, is advisable during prolonged therapy. Since **MYCLAV** contains amoxicillin, 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 a high incidence of rash if amoxicillin is used. **MYCLAV** should be given with caution to patients with lymphatic leukaemia since they are especially susceptible to amoxicillin-induced skin rashes.
- The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Aerobacter*, *Pseudomona*s or *Candida*), **MYCLAV** should be discontinued and/or appropriate therapy instituted.
- *Impaired hepatic function:* Changes in liver function test have been observed in some patients receiving **MYCLAV**. It should not be used in patients with evidence of severe hepatic dysfunction.
- *Impaired renal function*: In patients with moderate or severe renal impairment **MYCLAV** dosage should be adjusted (see **DOSAGE AND DIRECTIONS FOR USE**).
- The use of **MYCLAV** 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.

INTERACTIONS

Probenecid:

Probenecid decreases the renal tubular secretion of amoxicillin, but does not affect clavulanic acid excretion. Concurrent use with **MYCLAV** may result in increased and prolonged blood levels of amoxicillin, but not of clavulanic acid.

Oral contraceptives:

MYCLAV may reduce the efficacy of oral contraceptives and patients should be warned accordingly.

Allopurinol:

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

Antibiotics:

Tetracyclines and other bacteriostatic agents may interfere with the bactericidal effects of amoxicillin.

Anticoagulants, heparin or thrombolytic agents:

Increases in INR (prothrombin time) have been reported in patients taking **MYCLAV** concurrently with anticoagulants.

Nonsteroidal anti-inflammatory agents (NSAIDs):

A possible interaction may occur with concurrent use of NSAIDs (especially aspirin) and **MYCLAV**.

Methotrexate:

MYCLAV may reduce the excretion of methotrexate and cause a potential increase in methotrexate toxicity.

Interaction with laboratory tests:

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

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established.

Use in pregnancy:

The safety of **MYCLAV** in pregnancy has not been established.

Use in lactation:

Amoxicillin is distributed into breast milk. Although significant problems in humans have not been documented, the use of **MYCLAV** by breastfeeding mothers may lead to sensitisation, diarrhoea, candidiasis and skin rash in the infant. There is no data on the excretion of clavulanic acid in human milk.

DOSAGE AND DIRECTIONS FOR USE

Tablets should be taken immediately before a meal.

During the use of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to prevent any possibility of amoxicillin crystalluria.

Dosages:

General information: For infections caused by amoxicillin 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 **MYCLAV** is one **MYCLAV 375** tablet every eight hours at the start of a meal. For more severe infections and infections of the respiratory tract, the dose should be one **MYCLAV 625** tablet every eight hours at the start of a meal.

Since **MYCLAV 375** and **MYCLAV 625** tablets contain the same amount of clavulanic acid (125 mg as the potassium salt), two **MYCLAV 375** tablets are not equivalent to one **MYCLAV 625** tablet. Therefore, two **MYCLAV 375** tablets should not be substituted for one **MYCLAV 625** tablet for the treatment of more serious infections.

Impaired renal function:

Both amoxicillin 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 amoxicillin. The following schedule is proposed:

Creatinine clearance greater than 30 ml/minute:

- No dosage adjustment required.

Creatinine clearance 10 to 30 ml/minute:

- One **MYCLAV 375** or one **MYCLAV 625** tablet twice daily.

Creatinine clearance less than 10 ml/minute:

- One **MYCLAV 375** or one **MYCLAV 625** tablet once daily.

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

Dosage guide for adults:

Amoxicillin-sensitive organisms				
Product	Upper respiratory tract infections	Lower respiratory tract infections	Urinary tract infections	Skin and soft tissue infections
MYCLAV 375	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly
MYCLAV 625	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly

Amoxicillin-resistant organisms				
Product	Upper respiratory tract infections (otitis media) *H. influenzae, H. parainfluenzae*	Lower respiratory tract infections (bronchitis) *H. influenzae, H. parainfluenzae*	Urinary tract infections *E. coli, Klebsiella pneumoniae*	Skin and soft tissue infections *Staphylococcus aureus*
MYCLAV 625	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly

SIDE EFFECTS

Infections and infestations

Frequent: Mucocutaneous candidiasis.

Frequency unknown: Overgrowth of non-susceptible organisms.

Blood and lymphatic system disorders

Frequency unknown: Haemolytic anaemia, reversible thrombocytopenia, thrombocytopenic purpura, eosinophilia, reversible leucopenia (including neutropenia), agranulocytosis, platelet dysfunction.

Immune system disorders

Less frequent: Serum sickness-like syndrome, anaphylactic (hypersensitivity) reactions.

Frequency unknown: Hypersensitivity vasculitis, angioedema.

Nervous system disorders

Frequent: Headache, dizziness, tiredness.

Frequency unknown: Reversible hyperactivity, convulsions.

Gastrointestinal disorders

Frequent: Diarrhoea, nausea, vomiting, indigestion, abdominal pain, abnormal taste, gastritis, stomatitis, black 'hairy' tongue, enterocolitis, antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis).

Less frequent: Oral candidiasis.

Frequency unknown: *Clostridium difficile* colitis, glossitis.

Hepatobiliary disorders

Frequency unknown: Hepatitis, cholestatic jaundice, hepatic dysfunction.

Skin and subcutaneous tissue disorders

Frequent: Urticaria, pruritus, skin rashes.

Less frequent: Bullous exfoliative dermatitis, hives, itching, erythema multiforme.

Frequency unknown: Stevens-Johnson syndrome, acute generalised exanthematous pustulosis, toxic epidermal necrolysis.

Renal and urinary disorders

Frequency unknown: Interstitial nephritis, crystalluria, dysuria or urinary retention, proteinuria.

Reproductive system and breast disorders

Frequent: Vaginitis, genital moniliasis.

Less frequent: Vaginal candidiasis.

General disorders and administrative site conditions

Frequent: Hot flushes.

Frequency unknown: Chest pain, oedema, chills, fatigue, malaise, epistaxis.

Investigations

Less frequent: Moderate raise in aspartate transaminase (AST) and/or alanine transaminase (ALT).

Effects on the ability to drive and use machinery

Patients should be informed that **MYCLAV** may cause tiredness or dizziness and adversely affect their ability to drive or use machinery.

KNOWN SYMPTOMS OF OVERDOSE AND PARTICULARS OF ITS TREATMENT

Overdosage with **MYCLAV** 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.

Amoxicillin 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

MYCLAV 375: White, film coated, oval shaped, plain biconvex tablets.

Length of tablet 18,30 – 18,40 mm.

Width of tablet 8,30 – 8,40 mm.

MYCLAV 625: White, film coated, oval shaped, plain biconvex tablets.

Length of tablet 19,50 – 19,70 mm.

Width of tablet 9,50 – 9,70 mm.

PRESENTATION

Tablets are packed in aluminium foil blisters, each blister strip containing five tablets. Three blister strips are packed in an outer carton.

STORAGE INSTRUCTIONS

Store at or below 25 °C, protected from light and moisture.

Keep the blister strips in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

MYCLAV 375: A39/20.1.2/0068

MYCLAV 625: A39/20.1.2/0069

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

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