SCHEDULING STATUS

S4

1 NAME OF MEDICINE
CO MAUG ES 600 (Powder for oral suspension)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION CO MAUG ES 600
Each 5 mL reconstituted suspension contains amoxicillin trihydrate equivalent to 600 mg amoxicillin and potassium clavulanate equivalent to 42,90 mg clavulanic acid.
Contains sweetener:
Acesulfame Potassium: 9,6 mg / 5 ml Saccharin Sodium: 4,8 mg / 5 ml
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Powder for oral suspension.
CO MAUG ES 600 is a white to yellowish powder. After reconstitution it is an off-white to yellowish coloured homogenous suspension with strawberry flavour.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
CO MAUG ES 600 is indicated for the short-term treatment of acute bacterial otitis media infections when caused by the following CO MAUG ES 600 sensitive organisms: *Haemophilus influenzae*, *Streptococcus pneumoniae* (penicillin MIC ≤ 4 µg/mL) and *Moraxella catarrhalis*.

4.2 Posology and method of administration Posology
Duration of therapy should be appropriate to the indication and should not exceed 14 days without review.
The recommended dose for CO MAUG ES 600 is 90/6,4 mg/kg/day in 2 divided doses at 12 hourly intervals for 10 days, in children aged 3 months and older.
There is no experience in paediatric patients weighing >40 kg or in adults. There are no clinical data in children under 3 months of age.

Body Weight	Volume of CO MAUG ES 600 providing 90/6,4 mg/kg/day
8	3,0 mL twice daily
12	4,5 mL twice daily
16	6,0 mL twice daily
20	7,5 mL twice daily
24	9,0 mL twice daily
28	10,5 mL twice daily
32	12,0 mL twice daily
36	13,5 mL twice daily

Special populations
Hepatic Impairment
Dose with caution and monitor hepatic function at regular intervals. There are insufficient data on which to base a dosage recommendation.
Renal Impairment
There are no dosing recommendations for CO MAUG ES 600 in patients with renal impairment.

Method of administration
For oral use.
CO MAUG ES 600 should be taken immediately before a meal. For instructions on reconstitution see section 6.6.

4.3 Contraindications
CO MAUG ES 600 is contraindicated in:
- Hypersensitivity to amoxicillin or clavulanic acid or any of the excipients listed in section 6.1;
- Hypersensitivity to penicillins or cephalosporins. Cross-sensitivity between penicillins and cephalosporins is well documented;
- In patients with a previous history of amoxicillin/ clavulanic-associated jaundice/hepatic dysfunction.

Safety in children under 2 months of age has not been established. There are no clinical data in children under 3 months of age.

4.4 Special warnings and precautions for use
Prescribers must adhere to the principles of antibiotic stewardship.

Serious and occasionally fatal hypersensitivity (anaphylactic) and severe cutaneous reactions have been reported in patients on penicillin therapy. 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. Before initiating therapy with CO MAUG ES 600, careful analysis should be made regarding previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam allergens. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens.
Treatment with CO MAUG ES 600 should be terminated and the appropriate alternative therapy introduced in cases where an allergic reaction occurred. Serious anaphylactic reactions may require immediate emergency treatment with epinephrine (adrenaline). Oxygen, intravenous steroids, and airway management, including intubation might prove necessary.
CO MAUG ES 600 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.
Since CO MAUG ES 600 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 a morbilliform rash if amoxicillin is used. CO MAUG ES 600 should be avoided if infectious mononucleosis is suspected.
Prolonged use may result in overgrowth of non-susceptible organisms. The appropriateness of therapy should be demonstrated by means of sensitivity testing since use of antibiotics like CO MAUG ES 600 may lead to the selection of resistant strains of organisms.
CO MAUG ES 600 should be used in accordance with local official antibiotic prescribing guidelines and local susceptibility data.
Susceptibility to CO MAUG ES 600 will vary with geography and time. Local susceptibility data should be consulted where available and microbiological sampling and susceptibility testing performed where necessary.
It is important to consider that pseudomembranous enterocolitis has been reported with the use of antibiotics, especially in patients who develop diarrhoea during or after antibiotic use. It may range in severity from mild to life-threatening. Treatment should be discontinued, and the patient investigated further if prolonged or significant diarrhoea occurs or if the patient experiences abdominal cramps.
The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Aerobacter, Pseudomonas* or *Candida*).
CO MAUG ES 600 should be discontinued and/or appropriate therapy instituted. Abnormal prolongation of prothrombin time (increased international normalised ratio international normalised ratio (INR)) has been reported **[**~~rarely~~**]** in patients receiving
amoxicillin-clavulanate and oral anticoagulants.

Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.
CO MAUG ES 600 should be used with care in patients with evidence of hepatic dysfunction. Transient hepatitis and cholestatic jaundice have been reported. Changes in liver function tests have been observed in some patients receiving amoxicillin-clavulanic acid. It should be used with care in patients with evidence of severe hepatic dysfunction and hepatic function should be monitored at regular intervals (See Section 4.2).
Dosage of CO MAUG ES 600 should be adjusted in patients with moderate or severe renal impairment. The adjustment should be made according to the degree of impairment.
When high doses are administered, adequate fluid intake and urinary output must be maintained in order to reduce the possibility of amoxicillin crystalluria. Convulsions may occur in patients with impaired renal function or in those receiving high doses.
It is advisable to perform periodic assessment of organ system functions, including renal, hepatic and haematopoietic function, during prolonged therapy.
Since patients with lymphatic leukaemia are especially susceptible to amoxicillin-induced skin rashes, CO MAUG ES 600 should be given with caution.
The manifestation of a feverish generalised erythema associated with pustula at the onset of treatment may be a symptom of acute generalised exanthematous pustulosis (AGEP). This reaction necessitates CO MAUG ES 600 discontinuation and contraindicates any subsequent administration of amoxicillin.
It is recommended that when testing for the presence of glucose in urine during CO MAUG ES 600 treatment, enzymatic glucose oxidase methods should be used. Due to the high urinary concentrations of amoxicillin, false positive readings are common with chemical methods.
The presence of clavulanic acid in CO MAUG ES 600 may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.
In the treatment of infections caused by *Pseudomonas aeruginosa*, an aminoglycoside should be administered concomitantly.

4.5 Interaction with other medicines and other forms of interaction
Probenecid decreases the renal tubular secretion of amoxicillin but does not affect clavulanic acid excretion. Concurrent use with CO MAUG ES 600 may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid. Concomitant use of probenecid is not recommended.
The concomitant administration of allopurinol and ampicillin may increase the incidence of skin reactions in patients.
There is no data on amoxicillin-clavulanic acid and allopurinol administered concomitantly. Amoxicillin may reduce the excretion of methotrexate causing a potential increase in toxicity.
The prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of CO MAUG ES 600 in patients receiving acenocoumarol or warfarin concomitantly as cases of increased INR have been reported.
No information is available about the concurrent use of CO MAUG ES 600 and alcohol. However, the ingestion of alcohol whilst being treated with some other beta-lactam antibiotics has precipitated a disulfiram like reaction in some patients. Therefore. the ingestion of alcohol should be avoided during and for several days after treatment with CO MAUG ES 600.
CO MAUG ES 600 may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives. CO MAUG ES 600 may reduce the efficacy of oral contraceptives and patients should be warned accordingly.
In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid of approximately 50 % has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure.

4.6 Fertility, pregnancy and lactation Pregnancy
The safety of CO MAUG ES 600 during pregnancy has not been established and therefore the use of CO MAUG ES 600 during pregnancy is not recommended. In women with pre- term, premature rupture of the foetal membrane (pPROM), it was reported that prophylactic treatment with amoxicillin-clavulanate may be associated with an increased risk of necrotising enterocolitis in neonates.

Lactation
Amoxicillin is excreted into breast milk. The use of amoxicillin by nursing mothers may lead to sensitisation, diarrhoea, candidiasis and skin rash in the infant. Mothers on treatment with CO MAUG ES 600 should not breastfeed.

Fertility
No data available.

4.7 Effects on ability to drive and use machines
CO MAUG ES 600 may affect the ability of patients to drive or operate machines and caution is advised until the effects of CO MAUG ES 600 in patients on treatment are known (see section 4.8).

4.8 Undesirable effects
a. Tabulated summary of adverse reactions

System Organ Class	Frequency	Undesirable effect
Infections and infestations	*Frequent*	Mucocutaneous candidiasis (including vaginitis stomatitis and glossitis).
Blood and the lymphatic system disorders	*Less frequent*	Haemolytic anaemia, reversible thrombocytopenia, reversible leukopenia (including neutropenia) and agranulocytosis.
	Frequency unknown	Prolongation of bleeding time and prothrombin time.
Immune system disorders	*Less frequent*	Angioedema, anaphylaxis, serum sickness-like syndrome, hypersensitivity vasculitis.
	Frequent	Headache, fever, chills.
Nervous system disorders	*Less frequent*	Dizziness, hyperactivity, convulsions.
	Frequency unknown	Aseptic meningitis.
Gastrointestinal disorders	*Frequent*	Diarrhoea, nausea, vomiting. (Nausea is more often associated with higher oral dosages. If gastrointestinal reactions are evident, they may be reduced by taking CO MAUG ES 600 at the start of a meal)
	Less frequent	Indigestion, antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis).
	Frequency unknown	Superficial tooth discolouration (usually removed by brushing), black hairy tongue, abdominal pain, gastritis, stomatitis, glossitis, abnormal taste, tiredness, hot flushes.
Hepato-biliary disorders	*Less frequent*	Moderate rise in AST and/or ALT, hepatitis and cholestatic jaundice.
Skin and subcutaneous tissue disorders	*Less frequent*	Skin rashes, pruritis, urticaria, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative- dermatitis, acute generalised exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS).
Renal and urinary disorders	*Less frequent*	Crystalluria, interstitial nephritis.

b. Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose
Overdosage with amoxicillin 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 minimize the possibility of crystalluria, which can potentially lead to renal failure.
Amoxicillin may be removed from the circulation by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacological Classification: A 20.1.2 Penicillins.
Pharmacotherapeutic Group: Combinations of penicillins, including beta-lactamase inhibitors; ATC Code: J01CR02.
Amoxicillin/Clavulanic acid powder for oral suspension contains a broad-spectrum penicillin, **[**nl.**]** amoxicillin and potassium clavulanate. Clavulanic acid is a β-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range
of β-lactamase enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. It has good activity against the clinically important plasmid mediated β- lactamases frequently responsible for transferred drug resistance.
Amoxicillin shows bactericidal activity against both Gram-positive and Gram-negative organisms. Amoxicillin is, however, susceptible to degradation by β-lactamases and, therefore, the spectrum of activity does not include organisms which produce these enzymes. The clavulanic acid component has very little bactericidal action. It does however, by inactivation of susceptible β-lactamases, protect amoxicillin from degradation by a large number of β-lactamase enzymes produced by penicillin-resistant strains of organisms.
In vitro sensitivity does not necessarily imply *in vivo* efficacy.

Species for which acquired resistance may be a problem:
Gram-negative aerobes:
- *Escherichia coli*
- *Klebsiella oxytoca*
- *Klebsiella pneumoniae*
- *Klebsiella spp.*
- *Proteus mirabilis*
- *Proteus vulgaris*
- *Proteus spp.*
- *Salmonella spp.*
- *Shigella spp.*

Gram-positive aerobes:
- *Corynebacterium spp.*
- *Enterococcus faecium*

Inherently resistant organisms
Gram-negative aerobes:
- *Acinetobacter spp.*
- *Citrobacter freundii*
- *Enterobacter spp.*
- *Hafnia alvei*
- *Legionella pneumophila*
- *Morganella morganii*
- *Providencia spp.*
- *Pseudomonas spp.*
- *Serratia spp.*
- *Stenotrophomas maltophilia*
- *Yersinia enterolitica*

Others:
- *Chlamydia pneumoniae*
- *Chlamydia psittaci*
- *Chlamydia spp.*
- *Coxiella burnetti*
- *Mycoplasma spp.*

5.2 Pharmacokinetic properties Absorption
Amoxicillin and clavulanic acid are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration.
When taken at the start of a meal the absorption of amoxicillin/clavulanic acid is optimised. Amoxicillin serum concentrations achieved with amoxicillin-clavulanic acid combination are similar to those produced by oral administration of equivalent doses of amoxicillin alone. Following oral administration, the bioavailability of amoxicillin and clavulanic acid are approximately 70 %. For both components the plasma profiles are similar and in each case the time to peak plasma concentration (T_{max}) is approximately one hour.

Distribution
About 25 % of total plasma clavulanic acid and 18 % of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0,3 – 0,4 L/kg for amoxicillin and around 0,2 L/kg for clavulanic acid.
Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.

Elimination
The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms.
Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 L/h in healthy subjects. Approximately 60 to 70 % of the amoxicillin and approximately 40 to 65 % of the clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of single amoxicillin/ clavulanic acid 250 mg/125 mg or 500 mg/125 mg tablets. Urinary excretion for amoxicillin is between 50-85 % and between 27-60 % for clavulanic acid over a 24-hour period. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours after administration.
Clavulanic acid is extensively metabolised in man and the metabolites are eliminated in urine and faeces and as CO_2 in expired air.
Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid.

Age
The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm new-borns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. 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.

Renal impairment
The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function. The reduction in drug clearance is more noticeable for amoxicillin than for clavulanic acid, as a higher proportion of amoxicillin is excreted via the renal route. Doses in renal impairment must therefore prevent undue accumulation of amoxicillin while maintaining adequate levels of clavulanic acid.

Hepatic impairment
Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Acesulfame potassium
Carmellose sodium Crospovidone Type A Saccharin sodium
Silica colloidal anhydrous Silicon dioxide
Strawberry flavour (flavouring components, maize maltodextrin, propylene glycol, triethyl citrate)
Xanthan gum

6.2 Incompatibilities
Unknown

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store the powder for oral suspension at or below 25 °C.
Reconstituted suspensions should be stored in a refrigerator (2-8 °C) and used within 7 days.
Protect from light and moisture. SHAKE WELL BEFORE USE.
Keep out of reach of children.

6.5 Nature and contents of container
CO MAUG ES 600 is filled into an amber glass type III bottle with a nominal volume of 60 mL (for 30 mL oral suspension), 100 mL (for 50 mL or 70 mL oral suspension) or 150 mL (for 100 mL oral suspension), closed with a PP white screw cap containing a liner. The
liner can be of ALU or desiccant. The bottles are packed in a cardboard carton with a dosing device (6 mL PE/PS syringe, 5 mL or 10 mL PS spoon or a 5 mL PP cup).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling Instructions on reconstitution
For reconstitution tap the bottle until all the powder flows freely. Add approximately 2/3 of the total amount of water for reconstitution (see table below) and shake vigorously to suspend powder, add remainder of the water and again shake vigorously.

Strength	Amount of water to be added (ml)	Final amount of reconstituted oral suspension (ml)
600 mg/ 42,9 mg/5 ml	26	30
	43	50
	60	70
	85	100

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 HOLDERS OF CERTIFICATE OF REGISTRATION
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