AUGMENTIN BD

Professional Information

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

AUGMENTIN BD film-coated tablets

Amoxicillin 875 mg/Clavulanic acid 125 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each film-coated tablet contains amoxicillin trihydrate equivalent to 875 mg amoxicillin and potassium clavulanate equivalent to 125 mg clavulanic acid.

Sugar-free.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM:

Film-coated tablets.

White to off-white capsule-shaped, film-coated tablets, debossed with 'AC' on both sides with a score line on one side.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

AUGMENTIN BD are indicated for the treatment of infections caused by amoxicillin-resistant organisms producing β-lactamases sensitive to clavulanic acid:

- upper respiratory tract infections, such as sinusitis, recurrent otitis media, tonsillitis caused by Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis and Streptococcus pyogenes sensitive to AUGMENTIN BD
- lower respiratory tract infections, such as bronchitis and bronchopneumonia caused by Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis sensitive to AUGMENTIN BD
- genito-urinary tract infections, such as cystitis, urethritis, pyelonephritis caused by *Enterobacteriaceae (*mainly *Escherichia coli), Staphylococcus saprophyticus* and *Enterococcus species* skin and soft tissue infections caused by methicillin susceptible Staphylococcus aureus, Streptococcus pyogenes and Bacteroides species sensitive to AUGMENTIN BD

AUGMENTIN BD 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.

4.2 Posology and method of administration:

Posology:

Adult:

For more severe infections and infection of the respiratory tract, the dose should be one AUGMENTIN BD tablet every 12 hours at the start of a meal.

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.

AUGMENTIN BD should not be used in patients with a glomerular filtration rate of less than 30 mL/minute.

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

Posology Guide:

AMOXICILLIN-SENSITIVE ORGANISMS

PRODUCT	UPPER RESPIRATORY TRACT INFECTIONS	LOWER RESPIRATORY TRACT INFECTIONS	URINARY TRACT INFECTIONS	SKIN & SOFT TISSUE INFECTIONS
ADULTS:				
AUGMENTIN BD	1 tablet 12-hourly	1 tablet 12-hourly	1 tablet 12-hourly	1 tablet 12-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 & SOFT TISSUE INFECTIONS *Staphylococcus aureus*
ADULTS:				
AUGMENTIN BD	1 tablet 12-hourly	1 tablet 12-hourly	1 tablet 12-hourly	1 tablet 12-hourly

Method of administration:

Tablets should be taken immediately before a meal.

During the administration of AUGMENTIN BD, it is advisable to maintain adequate fluid intake and urinary output in order to prevent any possibility of amoxicillin crystalluria. (refer to section 4.9)

4.3 Contraindications:

Hypersensitivity to penicillins, cephalosporins or to any of the excipients listed in section 6.1. Cross-sensitivity between penicillins and cephalosporins is well documented.

AUGMENTIN BD is contraindicated in patients with a previous history of amoxicillin/clavulanic-associated jaundice/hepatic dysfunction (see section 4.8)

4.4 Special warnings and precautions for use:

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions have been reported in patients on penicillin therapy. Before initiating therapy with AUGMENTIN BD, 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. 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, AUGMENTIN BD should be discontinued and the appropriate therapy instituted. Serious anaphylactic reactions may require immediate emergency treatment with epinephrine (adrenaline).

Since AUGMENTIN BD 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 morbilliform rash if amoxicillin is used. AUGMENTIN BD should be avoided if infectious mononucleosis is suspected.

Prolonged use may result in overgrowth of non-susceptible organisms. Pseudomembranous enterocolitis has been reported and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further.
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*) the agent should be discontinued and/or appropriate therapy instituted.

Abnormal prolongation of prothrombin time (increased international normalised ratio (INR)) has been reported 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.

In patients with reduced urine output, crystalluria has been observed predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. (refer to section 4.9)

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 function, including renal, hepatic and haematopoietic functions, is advisable during prolonged therapy.

Impaired hepatic function: Changes in liver function tests have been observed in some patients receiving AUGMENTIN BD. Transient hepatitis and cholestatic jaundice has been reported. AUGMENTIN BD should be used with caution in patients with evidence of hepatic dysfunction.

Impaired renal function: In patients with moderate or severe renal impairment AUGMENTIN BD dosage should be adjusted (see section 4.2). AUGMENTIN BD should not be used in patients with a glomerular filtration rate of less than 30 mL/minute.

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

AUGMENTIN BD should be given with caution to patients with lymphatic leukaemia since they are especially susceptible to amoxicillin-induced skin rashes.

The use of AUGMENTIN BD 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.
AUGMENTIN BD should be used in accordance with local official antibiotic-prescribing guidelines and local susceptibility data.

Susceptibility to AUGMENTIN BD will vary with geography and time. Local susceptibility data should be consulted where available, and microbiological sampling and susceptibility testing performed where necessary.

4.5 Interactions 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 AUGMENTIN BD may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

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

The concomitant administration of allopurinol and amoxicillin 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.

Tetracyclines and other bacteriostatic drugs may interfere with the bactericidal effects of AUGMENTIN BD.

In the literature there are cases of INR in patients maintained on warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or INR should be carefully monitored with the addition or withdrawal of AUGMENTIN BD.

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.

Interaction with laboratory tests:

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

4.6 Fertility, pregnancy and lactation:

Pregnancy:

The safety of AUGMENTIN BD in pregnancy has not been established. 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 in the milk. There is no data on the excretion of clavulanic acid in human milk. Mothers on treatment with AUGMENTIN BD should not breastfeed their infants.

4.7 Effects on ability to drive or use machines:

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g., allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects:

Data from large clinical trials was used to determine the frequency of very common to rare undesirable effects. The frequencies assigned to all other undesirable effects (i.e., those

occurring at < 1/10 000) were mainly determined using post-marketing data and refer to a reporting rate rather than a true frequency.

Clinical Trial data:

The following convention has been used for the classification of frequency:

very common (≥ 1/10)

common (≥ 1/100, < 1/10)

uncommon (≥ 1/1 000, < 1/100)

rare (≥ 1/10 000, < 1/1 000)

very rare (< 1/10 000).

Infections and infestations:

Common: mucocutaneous candidiasis (including vaginitis, stomatitis and glossitis)

Blood and lymphatic system disorders:

Rare: reversible leucopenia (including neutropenia) and thrombocytopenia

Nervous system disorders:

Uncommon: dizziness, headache

Gastrointestinal disorders:

Very common: diarrhoea

Common: nausea, vomiting

Uncommon: indigestion, gastritis

The incidence and severity of adverse effects, particularly nausea and diarrhoea, increased with the higher recommended dose and can be minimised by administering AUGMENTIN BD at the start of a meal. In addition, as these symptoms are especially related to the potassium clavulanate component, where these gastrointestinal symptoms occur and a

higher concentration of amoxicillin is required, consideration should be given to administering the additional amoxicillin separately.

Hepatobiliary disorders:

Uncommon: A moderate rise in aspartate transaminase (AST) and/or alanine transaminase (ALT) has been noted in patients treated with AUGMENTIN BD.

The events may be severe and fatal. 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.

Skin and subcutaneous tissue disorders:

Uncommon: skin rash, pruritus, urticaria

Rare: erythema multiforme

Post-marketing spontaneous reports:

Blood and lymphatic system disorders:

Reversible agranulocytosis, haemolytic anaemia, prolongation of bleeding time and prothrombin time (increased INR).

Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly.

Immune system disorders:

Serious and occasional fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema can occur with oral penicillin (see section 4.4)

Angioedema, anaphylaxis, serum sickness-like syndrome, hypersensitivity vasculitis.

Nervous system disorders:

Reversible hyperactivity, aseptic meningitis, convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Gastrointestinal disorders:

Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) (see section 4.4).

Black 'hairy' tongue.

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

Hepatobiliary disorders:

Hepatitis and cholestatic jaundice. These events have been noted with other penicillins and cephalosporins.

Hepatic events may be severe and fatal occurring predominantly in males and elderly patients and may be associated with prolonged treatment. 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.

Skin and subcutaneous tissue disorders:

Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative-dermatitis, acute generalised exanthemous pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms (DRESS).

Whenever such reactions occur, AUGMENTIN BD should be discontinued.

Renal and urinary disorders:

Interstitial nephritis, crystalluria (refer to section 4.9).

Reporting of suspected adverse reactions:

Reporting suspected adverse events after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the '6.04 Adverse Drug Reaction Reporting form', found on line under SAHPRA 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 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.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Category A 20.1.2 Penicillins

Bactericidal action - The amoxicillin component of the formulations 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 β-lactamases, protect amoxicillin from degradation by a large number of β-lactamase enzymes produced by penicillin-resistant strains of organisms. Potassium clavulanate has been shown in vitro to be an irreversible inhibitor of beta-lactamases.

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 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:

The pharmacokinetics of amoxicillin and clavulanic acid are closely allied and neither are adversely affected by the presence of food in the stomach. After an oral dose of 2 parts amoxicillin and 1 part clavulanic acid, taken at the start of a meal, a mean peak serum level of 5,7 µg amoxicillin and 3,8 µg clavulanic acid per millilitre was achieved within one hour in healthy volunteers. Doubling the dose virtually doubles the peak serum level.

Excretion:

64,9 % of amoxicillin and 37,5 % of clavulanic acid are excreted unchanged in the urine in the first 6 hours after an oral dose of 2 to 1 amoxicillin/clavulanic acid tablets. Co-administration of probenecid has little effect on the excretion of the clavulanic acid component of the formulation.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

The tablet core contains colloidal anhydrous silica, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

The film-coat contains titanium dioxide (E171), hydroxypropyl methylcellulose, polyethylene glycol and silicone oil.

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

24 months

6.4 Special precautions for storage:

Store in a dry place at or below 30 °C.

DO NOT REMOVE DESICCANT.

Use within 14 days of opening.

6.5 Nature and contents of container:

The 10's pack consists of one aluminium pouch, containing a desiccant and a blister strip of 10 tablets packed into an outer carton. The blister is composed of a transparent PVC/PVdC laminate and grey aluminium foil.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

8. REGISTRATION NUMBERS:

32/20.1.2/0239

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

Date of registration:

07 April 1999

10. DATE OF REVISION OF TEXT

13 January 2021

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