APPROVED PACKAGE INSERT

AUGMENTIN TABLETS.

SCHEDULING STATUS:

S4

PROPRIETARY NAMES AND DOSAGE FORMS:

AUGMENTIN 375 tablets

AUGMENTIN 625 tablets

AUGMENTIN BD tablets

AUGMENTIN SR tablets

COMPOSITION:

AUGMENTIN 375: White/off-white, oval, film-coated tablets containing amoxicillin trihydrate equivalent to 250 mg amoxicillin and potassium clavulanate equivalent to 125 mg clavulanic acid.

AUGMENTIN 625: White/off-white, oval, film-coated tablets containing amoxicillin trihydrate equivalent to 500 mg amoxicillin and potassium clavulanate equivalent to 125 mg clavulanic acid.

AUGMENTIN BD: White/off-white, capsule-shaped, scored, film-coated tablets containing amoxicillin trihydrate equivalent to 875 mg amoxicillin and potassium clavulanate equivalent to 125 mg clavulanic acid.

AUGMENTIN SR : White, capsule-shaped, film-coated, bilayered tablets. Amoxicillin trihydrate equivalent to 562,5 mg amoxicillin and potassium clavulanate equivalent to 62,5 mg clavulanic acid are contained in the "Immediate Release" layer. Amoxicillin sodium equivalent to 437,5 mg amoxicillin is contained in the "Sustained Release" (SR) layer. The tablet strength is 1000 mg/ 62,5 mg, based on the overall amoxicillin/ clavulanate content.

PHARMACOLOGICAL CLASSIFICATION:

A 20.1.2 Penicillins

PHARMACOLOGICAL ACTION:

(a) Bacteriology:

(i) Spectrum - AUGMENTIN is the group name for formulations containing 2, 4, 7 and 16 parts of a broad spectrum penicillin, amoxicillin and 1 part of potassium clavulanate. Potassium clavulanate 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*. Potassium clavulanate 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).

(ii) 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.

AUGMENTIN SR is a sustained release tablet that provides an extended amoxicillin pharmacokinetic profile.

(b) 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 the 2 parts amoxicillin and 1 part clavulanic acid AUGMENTIN 375 tablet, taken at the start of a meal, a mean peak serum level of 5,7 ug amoxicillin and 3,8 ug clavulanic acid per millilitre was achieved within one hour in healthy volunteers. Doubling the dose virtually doubles the peak serum level.

(c) 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 AUGMENTIN 375 tablet. Co-administration of probenecid has little effect on the excretion of the clavulanic acid component of the formulation.

INDICATIONS:

AUGMENTIN formulations are 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.

AUGMENTIN formulations 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.

AUGMENTIN SR is indicated for the treatment of Respiratory Tract Infections, e.g. community-acquired pneumonia, acute exacerbations of chronic bronchitis and acute bacterial sinusitis, typically caused by *Streptococcus pneumoniae.*

CONTRA-INDICATIONS:

Hypersensitivity to penicillins or to cephalosporins. Cross-sensitivity between penicillins and cephalosporins is well documented.

AUGMENTIN is contra-indicated in patients with a previous history of amoxicillin/clavulanic-associated jaundice/hepatic dysfunction.

WARNINGS:

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. Before initiating therapy with AUGMENTIN, 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 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.

AUGMENTIN 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 rarely in patients receiving AUGMENTIN. 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. AUGMENTIN should be used with caution in patients with evidence of hepatic dysfunction.

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

AUGMENTIN SR is not recommended in patients with creatinine clearance < 30 ml/min and in haemodialysis patients.

INTERACTIONS:

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

AUGMENTIN 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 amoxicillin.

Interaction with laboratory tests:

It is recommended that when testing for the presence of glucose in urine during AUGMENTIN 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:

Use in pregnancy:

The safety of AUGMENTIN 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 amoxicillin 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.

During the administration 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.

Adult:

The adult dose for AUGMENTIN is one or two AUGMENTIN 375 tablet(s) every eight hours at the start of a meal. For more severe infections and infection of the respiratory tract, the dose should be one AUGMENTIN 625 tablet every eight hours at the start of a meal, or one AUGMENTIN BD tablet every 12 hours at the start of a meal.

AUGMENTIN SR is only indicated for use in adults, aged 16 or over. Two tablets of AUGMENTIN SR are to be taken orally twice a day.

Since AUGMENTIN 375, 625 and BD tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), two AUGMENTIN 375 tablets are not equivalent to one AUGMENTIN 625 tablet, and two AUGMENTIN 625 tablets are not equivalent to one AUGMENTIN BD. Therefore, two AUGMENTIN 375 tablets should not be substituted for one AUGMENTIN 625 tablet or two AUGMENTIN 625 tablets for one AUGMENTIN BD tablet for the treatment of more severe 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:

AUGMENTIN 375, 625:
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 twelve hours.

Severe impairment (creatinine clearance less than 10 ml/minute): half a tablet every twelve hours.

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.

AUGMENTIN SR

No adjustment in dosage is required in patients with creatinine clearance ≥30 ml/min. AUGMENTIN SR is not recommended in patients with creatinine clearance <30 ml/min. AUGMENTIN SR is not recommended in haemodialysis patients.

Dosage Guide:

AMOXICILLIN-SENSITIVE ORGANISMS

PRODUCT	UPPER RESPIRATORY TRACT INFECTIONS	LOWER RESPIRATORY TRACT INFECTIONS	URINARY TRACT INFECTIONS	SKIN & SOFT TISSUE INFECTIONS
ADULTS:				
AUGMENTIN 375	1 - 2 tablets 8-hourly	1 - 2 tablets 8-hourly	1 - 2 tablets 8-hourly	1 - 2 tablets 8-hourly
AUGMENTIN 625	1 tablet 8-hourly	1 tablet 8-hourly	1 tablet 8-hourly	1 tablet 8-hourly
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 375	2 tablets 8-hourly	2 tablets 8-hourly	1-2 tablets 8-hourly	1-2 tablets 8-hourly
AUGMENTIN 625	1 tablet 8- hourly	1 tablet 8-hourly	1 tablet 8-hourly	1 tablet 8-hourly
AUGMENTIN BD	1 tablet 12-hourly	1 tablet 12-hourly	1 tablet 12-hourly	1 tablet 12 hourly

AUGMENTIN SR:

Community acquired pneumonia	2 tablets 12-hourly for 7 to 10 days
Acute exacerbations of chronic bronchitis	2 tablets 12-hourly for 7 days
Acute bacterial sinusitis	2 tablets 12-hourly for 10 days

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, genital moniliasis, 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 minimised by administering AUGMENTIN 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.

The following adverse reactions have been reported and may occur with AUGMENTIN:

Hypersensitivity reactions:

Skin rashes, pruritis and urticaria, serum sickness-like syndrome, erythema multiforme, rare cases of Stevens-Johnson syndrome, hypersensitivity vasculitis and less frequently bullous exfoliative dermatitis, acute generalised exanthematous pustulosis (AGEP) and toxic epidermal necrolysis have been reported. Whenever such reactions occur, AUGMENTIN 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.

Gastrointestinal reactions:

Nausea, vomiting, diarrhoea, gastritis, stomatitis, glossitis, black 'hairy' tongue, enterocolitis, mucocutaneous candidiasis and antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis). If gastrointestinal reactions are evident, they may be reduced by taking AUGMENTIN 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 events are usually reversible. However, in extremely rare circumstances, death has been reported. These have almost always been cases associated with serious underlying disease or concomitant medication.

A moderate rise in aspartate transaminase (AST) and/or alanine transaminase (ALT) has been noted in patients treated with AUGMENTIN, but the significance of these findings is unknown.

Renal effects:

Crystalluria has been reported.

Haematological effects:

Haemolytic anaemia, reversible thrombocytopaenia, thrombocytopenic purpura, eosinophilia, reversible leucopenia (including neutropenia) 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 AUGMENTIN. Prolongation of bleeding time and prothrombin time have also been reported less frequently. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly.

CNS 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 especially with the suspension and chewable tablet formulations. It can usually be removed by brushing.

Special Precautions:

Caution is needed when administering amoxicillin 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 AUGMENTIN 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 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*, *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 AUGMENTIN. 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 AUGMENTIN dosage should be adjusted. (See DOSAGE AND DIRECTIONS FOR USE).

Use in lactation:

Amoxicillin is excreted in the milk; there is no data on the excretion of clavulanic acid in human milk. Therefore caution should be exercised when AUGMENTIN is administered to a nursing woman.

The use of AUGMENTIN 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 OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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.

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:

AUGMENTIN 375: White/off-white, oval, film coated tablets embossed with 'AUGMENTIN' on one side.

AUGMENTIN 625: White/off-white, oval, film coated tablets embossed with 'AC' and a score line on one side.

AUGMENTIN BD: White/off-white, capsule shaped, film-coated tablets, embossed 'A' and 'C' on both sides with a breakline on one side.

AUGMENTIN SR White, capsule-shaped, film-coated tablets, embossed with 'AC 1000/62.5' on one side and a bisect breakline on the other side.

PRESENTATION:

AUGMENTIN 375: The 15's pack consists of 3 aluminium pouches, each containing a desiccant and a blister strip of 5 tablets. The blister is composed of a transparent PVC/PVdC laminate and grey aluminium foil.

AUGMENTIN 625: The 15's pack consists of 3 aluminium pouches, each containing a desiccant and a blister strip of 5 tablets. The blister is composed of a transparent PVC/PVdC laminate and grey aluminium foil.

AUGMENTIN BD: The 10's pack consists of one aluminium pouch, containing a desiccant and a blister strip of 10 tablets. The blister is composed of a transparent PVC/PVdC laminate and grey aluminium foil.

AUGMENTIN SR: Aluminium/aluminium blister strips with one or two film-coated tablets per blister pocket.

STORAGE INSTRUCTIONS:

Store in a dry place at or below 25 ° C. Protect from light.

DO NOT REMOVE DESICCANT.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

AUGMENTIN 375 tablets	:	N/20.1.2/192
AUGMENTIN 625 tablets	:	28/20.1.2/0494
AUGMENTIN BD tablets	:	32/20.1.2/0239
AUGMENTIN SR tablets	:	36/20.1.2/0288

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Limited
57 Sloane Street
Bryanston
2021

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

27-02-2004

Botswana:

Augmentin BD tablets - Reg. No. BOT0400723 S2

Augmentin SR tablets - Reg. No. BOT0701010 S2

Namibia:

Augmentin BD tablets - Reg. No. 04/20.1.2/0897 NS2

Augmentin SR tablets - Reg. No. 04/20.1.2/1734 NS2

Zimbabwe:

Augmentin BD tablets - Reg. No. 2001/7.1.2/3960 PP