Professional Information (Proposed)

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

AUGMENTIN ES 600 Powder for Suspension Extra Strength

Amoxicillin 600 mg/Clavulanic acid 42,9 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Powder for suspension, when reconstituted according to instructions each 5 mL contains amoxicillin trihydrate BP equivalent to 600 mg amoxicillin and potassium clavulanate equivalent to 42,9 mg clavulanic acid. The amoxicillin is present as amoxicillin trihydrate and the clavulanic acid is present as potassium clavulanate in a ratio of 14:1

Sugar free.

Contains sweetener: Aspartame 13,60 mg/ 5 mL

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM:

Off-white powder for reconstitution.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications:

AUGMENTIN ES 600 is indicated for short term treatment of acute bacterial otitis media infections when caused by the following AUGMENTIN 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.

AUGMENTIN ES 600 is recommended for dosing at 90/6,4 mg/kg/day in two 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 (kg)	Volume of AUGMENTIN 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

AUGMENTIN ES 600 does not contain the same amount of clavulanic acid (as the potassium salt) as any of the other AUGMENTIN suspensions, therefore these suspensions should not be substituted for AUGMENTIN ES 600, as they are not interchangeable.

Hepatic impairment: There are insufficient data on which to base a dosage recommendation.

Renal impairment: There are no dosing recommendations for AUGMENTIN ES 600 in patients with renal impairment.

Method of administration

AUGMENTIN ES 600 should be taken immediately before a meal.

For instructions on dilution of the product before administration, see section 6.6.

4.3 Contraindications:

Hypersensitivity to penicillins, amoxicillin and cephalosporins or any other ingredient of AUGMENTIN ES 600.

AUGMENTIN ES 600 is contraindicated in patients with a previous history of AUGMENTIN-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:

Serious and occasionally fatal hypersensitivity reactions including anaphylaxis and severe cutaneous adverse 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. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to AUGMENTIN (see section 4.8).

Drug-induced enterocolitis syndrome has been reported mainly in children receiving amoxicillin-clavulanate (see section 4.8). Drug-induced enterocolitis syndrome is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after medicinal product administration) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, lethargy, diarrhoea, hypotension or leucocytosis with neutrophilia. In severe cases, drug-induced enterocolitis syndrome can progress to shock. 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 AUGMENTIN ES 600, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. If an allergic reaction occurs, AUGMENTIN ES 600 should be discontinued, and the appropriate alternative therapy instituted. Serious anaphylactic reactions require emergency treatment with epinephrine (adrenaline).

Since AUGMENTIN 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. AUGMENTIN ES 600 should be avoided if infectious mononucleosis is suspected.

Changes in liver function tests have been observed in some patients receiving AUGMENTIN ES 600. 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). Transient hepatitis and cholestatic jaundice have been reported. AUGMENTIN ES 600 should be used with caution in patients with evidence of hepatic dysfunction.

In patients with moderate or severe renal impairment AUGMENTIN ES 600 dosage should be adjusted according to the degree of impairment. (See Section 4.2)

Prolonged use may also result in overgrowth of non-susceptible organisms.
Pseudomembranous colitis has been reported with the use of antibiotics 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*), AUGMENTIN ES 600 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 use of this antibiotic 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 ES 600 should be used in accordance with local official antibiotic-prescribing guidelines and local susceptibility data.

Susceptibility to AUGMENTIN 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.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function, is advisable during prolonged therapy.

AUGMENTIN ES 600 should be given with caution to patients with lymphatic leukaemia since they are especially susceptible to amoxicillin induced skin rashes.

AUGMENTIN ES 600 contains aspartame and should be used with caution in patients with phenylketonuria.

4.5 Interactions with other medicines and other forms of interaction:

Concomitant use of probenecid is not recommended

Probenecid decreases the renal tubular secretion of amoxicillin but does not affect clavulanic acid excretion. Concomitant use with AUGMENTIN ES 600 may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

The concomitant administration of allopurinol and ampicillin could substantially increase 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. There is no data on AUGMENTIN ES 600 and allopurinol administered concomitantly.

No information is available about the concurrent use of AUGMENTIN 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 AUGMENTIN ES 600.

AUGMENTIN ES 600 may affect the gut flora, leading to lower oestrogen re-absorption and reduced efficacy of combined oral contraceptives. AUGMENTIN ES 600 may reduce the efficacy of oral contraceptives and patients should be warned accordingly

In the literature there are rare cases of increased international normalised ratio 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 amoxicillin.

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

Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

4.6 Fertility, pregnancy and lactation:

Use in Pregnancy

The safety of AUGMENTIN ES 600 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.

Use in lactation:

Amoxicillin is distributed into breast milk. There is no data on the excretion of clavulanic acid in human milk. Mothers on treatment with AUGMENTIN ES 600 should not breastfeed their infants

4.7 Effects on ability to drive and use machines:

No studies on the effects on ability to drive and use machines have been performed, however undesirable effects may occur which may influence the ability to drive and use machines.

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.

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

very common ≥1/10

common ≥1/100 to <1/10

uncommon ≥1/1 000 to <1/100

rare ≥1/10 000 to <1/1 000

very rare <1/10 000.

Clinical trial data:

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:

Common: Diarrhoea, nausea, vomiting.

Nausea is more often associated with higher oral dosages. If gastrointestinal reactions are evident, they may be reduced by taking AUGMENTIN ES 600 at the start of a meal.

Uncommon: Indigestion, gastritis

Hepatobiliary disorders:

Uncommon: A moderate rise in AST and/or ALT has been noted in patients treated with AUGMENTIN ES 600.

Skin and subcutaneous tissue disorders:

Uncommon: Skin rash, pruritus, urticaria.

Rare: Erythema multiforme

Post-marketing spontaneous reports:

Blood and lymphatic system disorders:

Reversible agranulocytosis and haemolytic anaemia. Prolongation of bleeding time and prothrombin time.(Refer to section 4.4).

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. (see also Skin and subcutaneous tissue disorders).

Nervous system disorders:

Reversible hyperactivity, aseptic meningitis and 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), drug-induced enterocolitis syndrome (see section 4.4).

Black “hairy” tongue

Superficial tooth discolouration has been reported which 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) (see also Immune system disorders).

If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued.

Linear IgA disease

Renal and urinary disorders:

Interstitial nephritis, crystalluria (refer to section 4.9)

Cardiac disorders:

Kounis syndrome (see section 4.4).

Reporting of suspected adverse rections:

Reporting suspected adverse events after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers (HCPs) are asked to report any suspected adverse reactions to SAHPRA via the Med safety APP (medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. HCPs can also report adverse events to GlaxoSmithKline's adverse event reporting line at aereporting.za@gsk.com, or phone at +27 (0) 10 300 1000.

4.9 Overdose:

Gastrointestinal symptoms (nausea, vomiting and diarrhoea) and disturbance of the fluid and electrolyte balances may be evident. They may be treated symptomatically, with attention to the water/electrolyte imbalance. AUGMENTIN ES 600 may be removed from the circulation by haemodialysis.

Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (refer to section 4.4).

5. PHARMACOLOGICAL PROPERTIES:

A 20.1.2 Penicillins

5.1 Pharmacodynamic Properties:

Bactericidal action - The amoxicillin component of the formulations exerts 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. 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 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:

The two components of AUGMENTIN ES 600, 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. Absorption of AUGMENTIN ES 600 is optimised when taken at the start of a meal. Amoxicillin serum concentrations achieved with the AUGMENTIN ES 600 combination are similar to those produced by the oral administration of equivalent doses of amoxicillin alone

Amoxicillin and clavulanic acid diffuse readily into most body tissues and fluids with the exception of the brain and spinal fluid. Neither amoxicillin nor clavulanic acid is highly protein bound, clavulanic acid is found to be approximately 25 % bound to human serum and amoxicillin approximately 18 % bound.

The major route of elimination for amoxicillin is the kidneys, whereas for clavulanic acid it is by both renal and non-renal mechanisms. Approximately 60-70 % of amoxicillin and 40-65 % clavulanic acid is excreted unchanged in urine during the first 6 hours after administration.

Amoxicillin is also partly excreted in the urine as the inactive metabolite (penicilloic acid) in quantities equivalent to 10-25 % of the initial dose. Clavulanic acid is extensively metabolised in man and the metabolites are eliminated in urine and faeces and as CO_2 in expired air.

Co-administration of probenecid has little effect on the excretion of the clavulanic acid component of the formulation, but delays amoxicillin excretion.

Pharmacokinetic studies performed in children, comparing AUGMENTIN ES 600 three times a day and twice daily formulations, indicate that the elimination pharmacokinetics seen in adults also apply to children with mature kidney function.

The mean AUC values for amoxicillin are essentially the same following twice-a-day dosing or three-times-a-day dosing, in adults. No differences between the b.i.d and t.i.d dosing regimes are seen when comparing the amoxicillin $T_{1/2}$, or C_{max} after normalisation for the different doses of amoxicillin administered. Similarly, no differences are seen for the clavulanate $T_{1/2}$, C_{max} or AUC values after appropriate dose normalisation.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of Excipients:

Aspartame, carboxymethylcellulose sodium 12, colloidal anhydrous silica, silicone dioxide, xanthan gum, and artificial strawberry cream flavour.

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

Powder for suspension in bottle: 2 years

Reconstituted suspensions should be stored at 2 °C to 8 °C (but not frozen) for up to 10 days.

6.4 Special precautions for storage:

AUGMENTIN ES 600 should be stored in a cool, dry place below 25 °C.

Keep the container tightly closed.

AUGMENTIN ES 600 suspension once reconstituted should be kept in a refrigerator (2 °C to 8 °C) and used within 10 days. Do not freeze. Discard unused suspension after 10 days.

6.5 Nature and contents of container:

Clear glass bottles with a pilfer proof or child resistant containing off-white powder for reconstitution to AUGMENTIN suspension extra strength.

6.6 Special precautions for disposal and other handling:

Before reconstitution shake the bottle to loosen powder.

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.

AUGMENTIN ES 600	
For reconstitution to (mL):	Amount of water to be added (mL):
50	50
75	70
100	90
150	135
After reconstitution , invert and shake bottle well before each use	

After reconstitution with water, an off-white to tan suspension with a characteristic strawberry odour.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

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Epping Industria 1, 7460

Tel. +27 (0) 10 300 1000

8. REGISTRATION NUMBER:

A39/20.1.2/0130

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

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