IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1077/093/009
Case No: 2043772

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

GlaxoSmithKline (Ireland) Ltd

Stonemasons Way, **Rathfarnham**, **Dublin 16**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Augmentin ES 600/42.9mg Powder for oral suspension

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **19/05/2008** until **09/11/2011**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Augmentin ES 600/42.9mg Powder for oral suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml of reconstituted suspension contains 600mg amoxicillin (as the trihydrate) and 42.9mg clavulanic acid (as the potassium salt)

Also contains Aspartame (E951) 13.60 mg

For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Powder for oral suspension
A free flowing, off-white powder with characteristic strawberry odour

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Indications:

Augmentin ES is indicated for short-term treatment of bacterial infections at the following sites when caused by Augmentin-susceptible organisms:

Upper respiratory tract infections e.g acute otitis media due to *Streptococcus pneumoniae* (including PRSP), *Haemophilus influenzae* and *Moraxella catarrhalis*; tonsillopharyngitis, and sinusitis typically caused by *Streptococcus pneumoniae* (including PRSP*), Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pyogenes*.

Lower respiratory tract infections e.g. lobar and broncho-pneumonia, typically caused by *Streptococcus pneumoniae* (including PRSP), *Haemophilus influenzae* and *Moraxella catarrhalis.*

Skin and soft tissue infections, typically caused by *Staphylococcus aureus* and *Streptococcus pyogenes*.

4.2 Posology and method of administration

Augmentin ES 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 on Augmentin ES in children under 3 months of age.

Augmentin ES does not contain the same amount of clavulanic acid (as the potassium salt) as any of the other Augmentin suspensions. Augmentin ES contains 42.9 mg of clavulanic acid per 5 ml whereas Augmentin 200 mg/5 ml suspension contains 28.5 mg of clavulanic acid per 5 ml and the 400 mg/5 ml suspension contains 57 mg of clavulanic acid per 5 ml. Therefore, the Augmentin 200 mg/5 ml and 400 mg/5 ml suspensions should not be substituted for Augmentin ES, as they are not interchangeable.

Renal impairment:
There are no dosage recommendations for patients with a creatinine clearance of $\leq$ 30 ml/minute.

Hepatic impairment:
Dose with caution, monitor hepatic function at regular intervals. There are insufficient data on which to base a dosage recommendation.

Method of administration

Augmentin ES is administered by the oral route.
To minimise potential gastrointestinal intolerance, administer at the start of a meal.
The absorption of clavulanic acid is enhanced when Augmentin ES is taken at the start of a meal.
Treatment should not be extended beyond 14 days without review.

4.3 Contraindications

Augmentin ES is contra-indicated in patients with a history of hypersensitivity to beta-lactams, e.g. penicillins and cephalosporins.

Augmentin ES is contra-indicated in patients with a previous history of Augmentin-associated jaundice/hepatic dysfunction.

4.4 Special warnings and precautions for use

Before initiating therapy with Augmentin ES careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens.

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity. If an allergic reaction occurs, Augmentin ES therapy should be discontinued and appropriate alternative therapy instituted. Serious anaphylactoid reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids and airway management, including intubation may also be required.

Augmentin ES 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 occasionally result in overgrowth of non-susceptible organisms.

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

Prolongation of prothrombin time has been reported rarely in patients receiving Augmentin ES. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly.

Augmentin ES should be used with caution in patients with evidence of hepatic dysfunction.

In patients with renal impairment, dosage of Augmentin should be adjusted according to the degree of impairment. No dosing recommendations can be made for Augmentin ES in renally impaired patients (see Section 4.2 Posology and method of administration).

In patients with reduced urine output, crystalluria has been observed very rarely, 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.

Augmentin ES suspension contains aspartame, which is a source of phenylalanine and so should be used with caution in patients with phenylketonuria. Each 5 mL of the Augmentin ES suspension contains 7 mg of phenylalanine.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use with Augmentin ES may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. There are no data on the concomitant use of Augmentin ES and allopurinol.

In common with other broad-spectrum antibiotics, Augmentin ES may reduce the efficacy of oral contraceptives and patients should be warned accordingly.

4.6 Pregnancy and lactation

Use in Pregnancy

Reproduction studies in animals (mice and rats at doses up to 10 times the human dose) with orally and parenterally administered Augmentin have shown no teratogenic effects. In a single study in women with preterm, premature rupture foetal membrane (pPROM), it was reported that prophylactic treatment with Augmentin ES may be associated with an increased risk of necrotising enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, unless considered essential by the physician.

Use in Lactation

Augmentin ES may be administered during the period of lactation. With the exception of the risk of sensitization, associated with the excretion of trace quantities in breast milk, there are no known detrimental effects for the breast-fed infant.

4.7 Effects on ability to drive and use machines

Adverse effects on the ability to drive or operate machinery have not been observed.

4.8 Undesirable effects

Approximately 14% of those patients who took Augmentin ES in the GSK clinical trial programme reported at least one adverse event that the investigator considered to be of suspected, or probable, relationship to the study medication.

Data from large clinical trials with Augmentin ES were 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 from all formulations of Augmentin 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 and <1/10, uncommon >1/1000 and <1/100, rare >1/10,000 and <1/1000, very rare <1/10,000.

Infections and infestations
Common Mucocutaneous candidiasis

Blood and lymphatic system disorders
Rare Reversible leucopenia (including neutropenia) and thrombocytopenia
Very rare Reversible agranulocytosis and haemolytic anaemia. Prolongation of bleeding time and prothrombin time (see Section 4.4 Special Warnings and Special Precautions for Use)

Immune system disorders
Very Rare Angioneurotic oedema, anaphylaxis, serum sickness-like syndrome, hypersensitivity vasculitis

Nervous system-disorders
Uncommon Dizziness, headache
Very Rare Reversible hyperactivity and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

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 at the start of a meal.

Uncommon Indigestion
Very Rare Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis). Superficial tooth discolouration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing.

Hepatobiliary disorders
Uncommon A moderate rise in AST and/or ALT has been noted in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown
Very Rare Hepatitis and cholestatic jaundice. These events have been noted with other penicillins and cephalosporins.

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children.

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. These are usually reversible. Hepatic events may be severe and in extremely rare circumstances, deaths have been reported. These have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have the potential for hepatic effects.

Skin and subcutaneous tissue disorders
Uncommon Skin rash, pruritus, urticaria
Rare Erythema multiforme
Very Rare Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative-dermatitis, acute generalised exanthemous pustulosis (AGEP)

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

Renal and urinary disorders
Very rare Interstitial nephritis, crystalluria

4.9 Overdose

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. They may be treated symptomatically, with attention to the water/electrolyte balance. Augmentin can be removed from the circulation by haemodialysis.

Amoxicillin crystalluria has been observed. (see Section 4.4 Special warnings and special precautions for use).

A prospective study of 51 paediatric patients at a poison control centre suggested that overdosages of less than 250 mg/kg of amoxicillin are not associated with significant clinical symptoms and do not require gastric emptying.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterial, ATC code: J01C R02

Amoxicillin is a semisynthetic antibiotic with a broad spectrum of bactericidal activity against many Gram-positive and Gram- negative microorganisms. Amoxicillin is, however, susceptible to degradation by beta-lactamases and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a beta-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of beta-lactamase enzymes commonly found in micro-organisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid mediated beta-lactamases frequently responsible for transferred drug resistance. It is generally less effective against chromosomally-mediated type 1 beta-lactamases.

The presence of clavulanic acid in Augmentin formulations protects amoxicillin from degradation by beta-lactamase enzymes and effectively extends the antibacterial spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other penicillins and cephalosporins. Thus Augmentin possesses the distinctive properties of a broad spectrum antibiotic and a beta-lactamase inhibitor.

Breakpoints

The MIC breakpoints (μg/ml) for Augmentin ES are shown in the following table:

Pathogen	MIC breakpoint (μg/ml) for Augmentin ES		
	S	**I**	**R**
S. pneumoniae	≤4/2	8/4	≥16/8
Haemophilus spp	≤4/2		≥8/4
Moraxella catarrhalis	≤4/2		≥8/4
Staphylococcus spp	≤4/2		≥8/4

Antibacterial spectrum
The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information gives only an approximate guidance on probabilities whether microorganisms will be susceptible to Augmentin ES or not. Where resistance patterns for a particular species are known to vary across the European Union, this is shown in the table below.

Microbial species	European range of acquired resistance for Augmentin ES when this is known to vary
Susceptible	
Gram-positive aerobes:	
Staphylococcus aureus (methicillin-susceptible, including β-lactamase-producing strains)*	0.00 – 9.84
Streptococcus pneumoniae (including penicillin-resistant strains (PRSP) with penicillin MIC ≤4μg/ml)*	1.47 –1.82
*Streptococcus pyogenes**	N/A
Gram-negative aerobes:	
Haemophilus influenzae (including β-lactamase-producing strains)*	0.00 – 0.29
Moraxella catarrhalis (including β-lactamase-producing strains)*	0.00
Resistant	
Gram-positive aerobes	
Methicillin-resistant staphylococci (MRSA/MRSE)	N/A
Gram-negative aerobes	
Pseudomonas aeruginosa	N/A

Stenotrophomonas multophilia	N/A
Acinetobacter spp	N/A
Serratia spp	N/A
Citrobacter spp	N/A
Anaerobes	
Clostridium difficile	N/A
Atypical organisms	
Mycoplasma pneumoniae	N/A

N/A= not applicable
*Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications
Cross-resistance: Amoxicillin on its own may show cross-resistance to other beta-lactams, beta-lactam/beta-lactamase inhibitor combinations, and cephalosporins depending on the frequency of the diverse mechanism of resistance in the different pathogens. In the case of alteration of the target (the penicillin-binding proteins [PBPs]) as in *S. pneumoniae*, only the isolates with high resistance to penicillin are likely to show cross-resistance to amoxicillin. These isolates with resistance to amoxicillin show a high proportion of cross-resistance to macrolides and virtually to all second-generation cephalosporins.
Amoxicillin/clavulanic acid can have activity against the plasmid-encoded beta-lactamases known as the extended spectrum beta-lactamases (ESBL) that are produced primarily by *K. pneumoniae* and *E. coli*. Enzymes TEM-3 to TEM-26 and SHV-2 to SHV-6 are included in this group, and confer resistance to the second- and third-generation cephalosporins and monobactams. The metalloenzymes are another group of plasmid-mediated beta-lactamases found in *S. maltophilia*, *Aeromonas* sp., *B. cepacea*, *B. fragilis*, *S. marcescens*, and *P. aeruginosa*. The current beta-lactamase inhibitors are not active against these enzymes. The chromosomally-encoded or inducible beta-lactamases of the AmpC class can be found in *Enterobacter*, *Citrobacter*, *Morganella*, *Serratia*, *Providencia*, and *Pseudomonas aeruginosa*. Resistance is seen in the first-, second-, and third-generation cephalosporins and beta-lactam/beta-lactamase inhibitor combinations including amoxicillin/clavulanic acid. The penicillinases of the gram-positive organism, *S. aureus*, are not active against clavulanic acid.
Resistance Mechanisms: Clavulanic acid protects against resistance mediated by certain plasmid-encoded beta-lactamase enzymes (TEM-1, TEM-2, SHV-1) common in some strains of *Escherichia*, *Shigella*, *Salmonella*, *Proteus* and *Klebsiella*. Similarly, clavulanic acid maintains its activity against ESBL. Nevertheless, clavulanic acid would not adequately protect amoxicillin against isolates with metallo-enzymes, or inducible or chromosomally-encoded beta-lactamase enzymes. The high amoxicillin content of Augmentin ES improves efficacy against organisms with resistance mediated by modified pencillin-binding proteins (PBPs).

5.2 Pharmacokinetic properties

a. Absorption:
The two components, of Augmentin, 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 clavulanic acid is enhanced when Augmentin is taken at the start of a meal.

b. Pharmacokinetics

Pharmacokinetic parameters (mean ± SD)* are given below for Augmentin ES administered at 45 mg/kg every 12 hours to paediatric patients

Formulation	**C_{max} (mg/l)**	**t_{max*} (hours)**	**$AUC_{(0-t)}$ (mg.h/l)**	**$t_{½}$ (hours)**
Augmentin ES 600/42.9 mg/5ml (14:1) Dosed at 45 mg/kg amoxicillin 12-hourly	***Amoxicillin***			
	15.7 ± 7.7	2.0 (1.0 – 4.0)	59.8 ± 20.0	1.4 ± 0.3
	Clavulanic acid			
	1.7 ± 0.9	1.1 (1.0 – 4.0)	4.0 ± 1.9	1.1 + 0.3

* median and range provided for t_{max}

Amoxicillin serum concentrations achieved with Augmentin are similar to those produced by the oral administration of equivalent doses of amoxicillin alone.

Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (see Section 4.5, Interaction with other medicaments and other forms of interaction).

c. Distribution:
Following intravenous administration therapeutic concentrations of both amoxicillin and clavulanic acid may be detected in the tissues and interstitial fluid. Therapeutic concentrations of both drugs have been found in gall bladder, abdominal tissue, skin, fat, and muscle tissues; fluids found to have therapeutic levels include synovial and peritoneal fluids, bile and pus.

Neither amoxicillin nor clavulanic acid is highly protein bound, studies show that about 25% for clavulanic acid and 18% for amoxicillin of total plasma drug content is bound to protein. From animal studies there is no evidence to suggest that either component accumulates in any organ.

Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanate can also be detected in breast milk. With the exception of the risk of sensitisation associated with this excretion, there are no known detrimental effects for the breast-fed infant.

Reproduction studies in animals have shown that both amoxicillin and clavulanic acid penetrate the placental barrier. However, no evidence of impaired fertility or harm to the foetus was detected.

d. Elimination:
As with other penicillins, the major route of elimination for amoxicillin is via the kidney, whereas for clavulanate it is by both renal and non-renal mechanisms. Approximately 60-70% of the amoxicillin and approximately 40-65% of the clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of a single 250/125 mg or a single 500/125 mg tablet.

Amoxicillin is also partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to 10-25% of the initial dose. Clavulanic acid is extensively metabolized in man to 2,5-dihydro-4-(2- hydroxyethyl)-5-oxo-1H-pyrrole-3-carboxylic acid and 1-amino-4-hydroxy- butan-2-one and eliminated in urine and faeces as carbon dioxide in expired air.

5.3 Preclinical safety data

No further information of relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silica, colloidal anhydrous
Carboxymethylcellulose Sodium 12
Aspartame (E 951)
Xanthan gum
Silicon dioxide
Artificial strawberry cream flavour

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

Dry powder:

18 months

Suspension:

After reconstitution use for maximum 10 days

6.4 Special precautions for storage

Dry powder:
Do not store above 25oC. Keep the container tightly closed.

Suspension:
Once reconstituted, store at 2°C to 8°C. Do not freeze.

6.5 Nature and contents of container

Clear glass bottles (Type III) closed with an aluminium closure with PVC liner. A measuring cup is provided in each pack.
Bottle sizes of 20ml, 50 ml, 75 ml, 100 ml and 150 ml. The bottle pack is placed in a cardboard carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Tap 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	
Bottle Size (ml)	**Amount of Water Required for Suspension (ml)**
20	19
50	50
75	70
100	90
150	135

Each 5 ml of reconstituted suspension contains 600 mg amoxicillin as the trihydrate and 42.9 mg of clavulanic acid as the potassium salt.

Note: SHAKE ORAL SUSPENSION WELL BEFORE USING.

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Ltd
Stonemasons Way
Rathfarnham
Dublin 16

8 MARKETING AUTHORISATION NUMBER

PA1077/93/9

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 10th November 2006

10 DATE OF REVISION OF THE TEXT