Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Augmentin 1000/62.5mg film coated prolonged release tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablet containing 1000mg amoxicillin, 562.5mg as amoxicillin trihydrate, and 437.5mg as amoxicillin sodium and 62.5mg clavulanic acid as potassium clavulanate (16:1).

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet

A white capsule shaped film coated tablet debossed with 1000/62.5 on one side and a bisect break line on the other.

4 CLINICAL PARTICULARS

General description
Amoxicillin-clavulanate SR (the beta-lactam antibacterial amoxicillin coformulated with the beta-lactamase inhibitor clavulanate) is an antibiotic agent with a notably broad spectrum of activity against the commonly-occurring bacterial pathogens in general and hospital practice. The beta-lactamase inhibitory action of clavulanate extends the spectrum of amoxicillin to embrace a wider range of organisms, including many resistant to other beta-lactam antibiotics. Amoxicillin-clavulanate SR is a sustained release tablet that provides an extended amoxicillin pharmacokinetic profile. The Amoxicillin-clavulanate SR formulation extends the spectrum of Amoxicillin-clavulanate to include the majority of *S. pneumoniae* where resistance is mediated by penicillin-binding proteins (penicillin-resistant *S. pneumoniae*, or PRSP).

4.1 Therapeutic Indications

Amoxicillin-clavulanate SR is indicated for short-term treatment of bacterial infections at the following sites when caused by amoxicillin-clavulanate SR-susceptible organisms:
Respiratory Tract Infections, e.g. community-acquired pneumonia, acute exacerbations of chronic bronchitis and acute bacterial sinusitis, typically caused *by Streptococcus pneumoniae* (including penicillin-resistant *S. pneumoniae* - PRSP*), Haemophilus influenzae*[#], *Moraxella catarrhalis*[#] and *Streptococcus pyogenes*.
([#]Some members of these species of bacteria produce beta-lactamase, rendering them non-susceptible to amoxicillin alone).
A comprehensive list of susceptible organisms is provided in Clinical Pharmacology, Pharmacodynamics.
Infections caused by amoxicillin-susceptible organisms are amenable to amoxicillin-clavulanate SR treatment due to its amoxicillin content.

Mixed infections caused by amoxicillin-susceptible organisms in conjunction with amoxicillin-clavulanate-susceptible beta-lactamase-producing organisms may therefore by treated by amoxicillin-clavulanate SR. Amoxicillin-clavulanate SR has been shown to be effective against strains of *S. pneumoniae* resistant to penicillin (penicillin MIC greater than or equal to 2 mg/l) (*see Clinical Pharmacology, Pharmacodynamics*).

4.2 Posology and method of administration

Administer amoxicillin-clavulanate SR at the start of a meal to optimise absorption.
Treatment should not be extended beyond 14 days without review.

Populations

- **Adults (greater than or equal to 16 years)**

Respiratory tract infections: two tablets twice daily for seven to ten days, Including:

Community acquired pneumonia	Two tablets twice daily for seven to ten days
Acute exacerbations of chronic bronchitis	Two tablets twice daily for seven days
Acute bacterial sinusitis	Two tablets twice daily for ten days

- **Children**

Amoxicillin-clavulanate SR is indicated for use in adults greater than 16 years only.

- **Elderly**

No adjustment needed.

- **Renal Impairment**

No adjustment in dosage is required in patients with creatinine clearance greater than or equal to 30 ml/min.
Amoxicillin-clavulanate SR is not recommended in patients with creatinine clearance less than 30 ml/min.

- **Haemodialysis**

Amoxicillin-clavulanate SR is not recommended in haemodialysis patients

- **Hepatic Impairment**

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

4.3 Contraindications

Amoxicillin-clavulanate SR is contraindicated:

- In patients with a history of hypersensitivity to beta-lactams, e.g. penicillins and cephalosporins.
- In patients with a previous history of amoxicillin-clavulanate-associated jaundice/hepatic dysfunction.

4.4 Special warnings and precautions for use

Before initiating therapy with amoxicillin-clavulanate SR, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins or cephalosporins.

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, amoxicillin-clavulanate SR therapy must be discontinued and appropriate alternative therapy instituted. Serious anaphylactoid reactions require immediate emergency treatment with adrenaline. Oxygen, i.v. steroids and airway management (including intubation) may also be required.
Amoxicillin-clavulanate SR 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 also occasionally result in overgrowth of non-susceptible organisms.
Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin-clavulanate. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly.

No adjustment in amoxicillin-clavulanate SR dosage is required in patients with creatinine clearance greater than or equal to 30 ml/min. Amoxicillin-clavulanate SR is not recommended in patients with creatinine clearance less than 30 ml/min.
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.
Amoxicillin-clavulanate SR should be used with caution in patients with evidence of hepatic dysfunction.

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 amoxicillin-clavulanate may result in increased and prolonged blood levels of amoxicillin, but no of clavulanate 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 amoxicillin-clavulanate and allopurinol.

In common with other antibiotics, amoxicillin-clavulanate may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

4.6 Pregnancy and lactation

Pregnancy

Reproduction studies in animals (mice and rats at doses up to 10 times the human dose) with orally and parenterally administered amoxicillin-clavulanate have shown no teratogenic effects. In a single study in women with preterm, 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. As with all medicines, use should be avoided in pregnancy, unless considered essential by the physician.

Lactation

Amoxicillin-clavulanate may be administered during the period of lactation. With the exception of the risk of sensitisation, 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

None known.

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 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 Genital monialiasis, 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 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, convulsions

Gastrointestinal disorders
Very common Diarrhoea
Common Nausea, abdominal pain
Uncommon Vomiting, indigestion
Very rare Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis).
Black hairy tongue

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.
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

Symptoms and Signs
Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident.
Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (*see section 4.4 Special warnings and Precautions for use*).

Treatment
GI symptoms may be treated symptomatically, with attention to the water/electrolyte balance.
Amoxicillin-clavulanate can be removed from the circulation by haemodialysis.

Drug abuse and dependence
Drug dependence, addiction and recreational abuse have not been reported as a problem with this compound.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action:
Amoxicillin is a semisynthetic antibiotic with a broad spectrum of antibacterial 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.

Clavulanate 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 clavulanate in AUGMENTIN SR 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 SR possesses the distinctive properties of a broad-spectrum antibiotic and a beta-lactamase inhibitor. AUGMENTIN SR is a sustained release tablet that provides an extended amoxicillin pharmacokinetic profile. The amox-clav-SR formulation extends the spectrum of amox-clav to include the majority of *S. pneumoniae* where resistance is mediated by penicillin binding proteins (penicillin-resistant *S. pneumoniae* or PRSP).
Microbiology: AUGMENTIN SR is bactericidal to a wide range of organisms (see susceptibility table below).

Breakpoints	**Susceptible**	**Intermediate**	**Resistant**
Streptococcus pneumoniae	≤ 4 mg/l	8 mg/l	≥ 16 mg/l
Haemophilus influenzae	≤ 4/2 mg/l	-	≥ 8/4 mg/l
Moraxella catarrhalis	≤ 4/2 mg/l	-	≥ 8/4 mg/l
Staphylococcus aureus (MSSA)[#]	≤ 4/2 mg/l	-	≥ 8/4 mg/l
Klebsiella pneumoniae[#]	≤ 8/4 mg/l	16/8mg/l	≥ 32/16 mg/l

Susceptibility

Susceptible aerobes gram-positive
Staphylococcus aureus (MSSA)[#] *
Staphylococcus epidermidis MSSE)[#]
Streptococcus pneumoniae (including PRSP & macrolide-resistant) *
Streptococcus pyogenes *
Viridans Group *Streptococcus* *

Susceptible anaerobes gram-positive
Peptostreptococcus anaerobius
Peptostreptococcus magnus
Peptostreptococcus micros

Susceptible aerobes gram-negative
Haemophilus influenzae[#] *
Haemophilus parainfluenzae[#] *
Klebsiella pneumoniae[#] *
Moraxella catarrhalis[#] *

Susceptible anaerobes gram-negative
Bacteroides fragilis[#]
Eikenella corrodens[#]
Fusobacterium nucleatum[#]
Porphyromonas sp.
Prevotella sp.

Some members of these species of bacteria produce β-lactamase, rendering them non-susceptible to amoxicillin alone.
* Bacteriological eradication shown in clinical studies

Other Information

Cross-resistance: Amoxicillin on its own shows cross-resistance to other beta-lactams, beta-lactam/beta-lactamase inhibitor combinations, and cephalosporins.
Resistance Mechanisms: Clavulanate protects against resistance mediated by certain beta-lactamase enzymes. The sustained-release formulation of AUGMENTIN SR improves efficacy against organisms with resistance mediated by modified pencillin-binding proteins (PBPs).

5.2 Pharmacokinetic properties

Absorption
The two components of amoxicillin-clavulanate SR (amoxicillin and clavulanate) are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration.

Absorption of amoxicillin-clavulanate SR is optimised when taken at the start of a meal.

The pharmacokinetic results that have been obtained for amoxicillin and clavulanate following the administration of amoxicillin-clavulanate SR 2 x 1000/62.5 mg to healthy adults at the start of a meal are presented below:

Mean pharmacokinetic parameters						
Drug administered	**Dose (mg)**	**T>MIC^ h (%)**	**Cmax (mg/l)**	**Tmax (h)**	**AUC (ug.h/ml)**	**T1/2 (h)**
Amoxicillin						
Amoxicillin-clavulanate SR 1000/62.5 mg x 2	2000	5.9 (49.4)	17.0	1.50	71.6	1.27
Clavulanate						
Amoxicillin-clavulanate SR 1000/62.5 mg **x2**	125	ND	2.05	1.03	5.29	1.03
ND – Not determined ^ for an MIC of 4 mg/l						

The amoxicillin-clavulanate SR sustained release formulation has an unique PK/PD profile. The T>MIC obtained with amoxicillin-clavulanate SR can not be achieved with the same dose formulated as an immediate release tablet.

Distribution
Following i.v. administration of amoxicillin/clavulanate, therapeutic concentrations of both amoxicillin and clavulanate 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 clavulanate is highly protein-bound, studies show that about 25% for clavulanate 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 clavulanate penetrate the placental barrier. However, no evidence of impaired fertility or harm to the foetus was detected.

Metabolism
Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25% of the initial dose. Clavulanate 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, and as carbon dioxide in expired air.

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.
Previous studies have shown that, on average, up to approximately 60 to 70% of the amoxicillin and approximately up to 40 to 65% of the clavulanate are excreted unchanged in the urine.
Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanate (*see section 4.5 Interaction with other medicinal products and other forms of interction*).

5.3 Preclinical safety data

No further information of relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Sodium starch glycollate
Colloidal anhydrous silica
Magnesium stearate
Xantham gum
Citric acid

Film coat (opadry YS 1 7700):
Hypromellose 6cp
Hypromellose 15cp
Titanium dioxide (E171)
Macrogol 3350
Macrogol 8000

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.
Store in original package.

6.5 Nature and contents of container

PVC/aluminium or aluminium/aluminium blister strips with one film-coated tablet per blister pocket and 2 x 2 tablets per blister. Packs of 28 tablets.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited,
Stonemasons way,
Rathfarnham,
Dublin 16.

8 MARKETING AUTHORISATION NUMBER

PA0678/012/008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 February 2005

10 DATE OF REVISION OF THE TEXT

September 2006