IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA1077/093/006
Case No: 2064670

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

GlaxoSmithKline (Ireland) Limited

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

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

Augmentin Junior 125mg/62.5mg per 5ml 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 **08/02/2010**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Augmentin Junior 125mg/62.5mg per 5ml Powder for Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of reconstituted suspension contains Amoxicillin Trihydrate equivalent to 125 mg of amoxicillin and potassium clavulanate equivalent to 62.5 mg of clavulanic acid.

Excipient: Each 5ml of reconstituted oral suspension contain 12.5mg of aspartane (E951)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for oral suspension
White to off-white powder for reconstitution with water.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Augmentin is indicated for short term treatment of bacterial infections at the following sites when amoxicillin resistant beta-lactamase producing strains are suspected as the cause. In other situations, amoxicillin alone should be considered.

Upper Respiratory Tract Infections (including ENT) in particular sinusitis, otitis media, recurrent tonsillitis. These infections are often caused by *Streptococcus pneumoniae, Haemophilus influenzae**, *Moraxella catarrhalis** and *Streptococcus pyogenes.*

Lower Respiratory Tract Infections in particular acute exacerbations of chronic bronchitis (especially if considered severe), bronchopneumonia. These infections are often caused by *Streptococcus pneumoniae, Haemophilus influenzae** and *Moraxella catarrhalis*.*

Genito-urinary Tract and Abdominal Infections in particular cystitis (especially when recurrent or complicated - excluding prostatitis), septic abortion, pelvic or puerperal sepsis and intra-abdominal sepsis. These infections are often caused by Enterobacteriaceae* (mainly *Escherichia coli**), *Staphylococcus saprophyticus,* Enterococcus species.*

Skin and Soft Tissue Infections in particular cellulitis, animal bites and severe dental abscess with spreading cellulitis. These infections are often caused by *Staphylococcus aureus*, Streptococcus pyogenes* and Bacteroides species*.

* Some members of these species of bacteria produce beta-lactamase, rendering them insensitive to amoxicillin alone.

Augmentin Intravenous is indicated when parenteral therapy is required.

A comprehensive list of sensitive organisms is provided in Pharmacodynamic properties.

Mixed infections caused by amoxicillin-susceptible organisms in conjunction with Augmentin-susceptible beta-lactamase-producing organisms may be treated with Augmentin. These infections should not require the addition of another antibiotic resistant to beta-lactamases.

4.2 Posology and method of administration

Usual dosages in the treatment of infection:

Children 6-12 years
The usual dosage is 187 mg (5 ml) three times daily.
In severe infections these doses may be doubled.
This formulation is not recommended for children under the age of 6 years.

Renal impairment
In patients with moderate or severe renal impairment dosages should be adjusted according to the degree of impairment.

Creatinine clearance ml/min	Dosage mg	Interval hr
10 - 30	15/3.75* mg/kg *(maximum 500/125mg twice daily)*	12 (b.i.d., twice a day)
< 10	15/3.75* mg/kg *(maximum 500/125mg)*	24 (o.d., once a day)

* using the Paediatric Suspension

Haemodialysis
Dosage adjustments are based on the maximum recommended level of amoxicillin.15/3.75 mg/kg/day given as a single dose. One additional dose of 15/3.75 mg/kg should be administered prior to haemodialysis and again after haemodialysis.

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

Administration:
Oral: Suspension.

To minimise potential gastro-intestinal intolerance administer at the start of a meal. The absorption of Augmentin is optimised when taken at the start of a meal.

Duration of therapy should be appropriate to the indication and should not exceed 14 days without review.

4.3 Contraindications

Use in patients with a history of hypersensitivity to beta-lactams e.g. penicillins and cephalosporins. Augmentin 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 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 (see Contra-indications).

Augmentin should be used with caution in patients with evidence of hepatic dysfunction and with care in patients with renal dysfunction when dosage should be adjusted (see 4.2).

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 of an anti-infective agent may result in superinfection by microorganisms including candida resistant to that anti-infective.

Augmentin Suspensions contain 12.5 mg aspartame per 5 ml dose and therefore care should be taken in phenylketonuria. Each 5 ml dose contains 0.31 mmol of potassium (Junior Suspension).

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 (see Overdosage).

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 not of clavulanic acid.

Prolongation of bleeding time and prothrombin time have been reported in some patients receiving Augmentin. Augmentin should be used with care in patients on anti-coagulation therapy.

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

Use in pregnancy:
Reproduction studies in animals (mice and rats) with orally and parenterally administered Augmentin 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 Augmentin 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 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

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

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: 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
Very common: Diarrhoea.

Common: Nausea, vomiting.
Nausea is often associated with higher oral doses. 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.
Black hairy tongue

Hepatobiliary disorders
Uncommon: A moderate rise in AST and/or ALT and Alkaline Phosphates 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 predominately 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.

Skin and subcutaneous tissue disorders
Uncommon: Skin rash, pruritis, 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 (see Overdosage).

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 fluid and electrolyte balance. Clavamel may be removed from the circulation by haemodialysis. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see Section 4.4 special warnings and special precautions for use).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combination antibacterials.
ATC code: J01RA01.

Augmentin is an antibiotic agent with a notably broad spectrum of activity against the commonly occurring bacterial pathogens in general practice and hospital. 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 lactamase antibiotics.

Resistance to many antibiotics is caused by bacterial enzymes which destroy the antibiotic before it can act on the pathogen. The clavulanate in Augmentin anticipates this defence mechanism by blocking the beta-lactamase enzymes, thus rendering the organisms sensitive to amoxicillin rapid bactericidal effect at concentrations readily attainable in the body.

Clavulanate by itself has little antibacterial activity; however, in association with amoxicillin as Augmentin, it produces an antibiotic agent of broad spectrum with wide application in hospital and general practice.

Augmentin is bactericidal to a wide range of organisms including:

Gram-positive:
Aerobes: *Enterococcus faecalis*, Enterococcus faecium*, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus viridans, Staphylococcus aureus*, Coagulase negative staphylococci* (*including *Staphylococcus epidermidis*),* Corynebacterium species*, Bacillus anthracis*, Listeria monocytogenes.*

Anaerobes: Clostridium species, Peptococcus species, Peptostreptococcus.

Gram-negative:
Aerobes: *Haemophilus influenzae*, Moraxella catarrhalis* (Branhamella catarrhalis), Escherichia coli*, Proteus mirabilis*, Proteus vulgaris**, Klebsiella species***, Salmonella species***, Shigella species***, *Bordetella pertussis,* Brucella species, *Neisseria gonorrhoeae*, Neisseria meningitidis*, Vibrio cholerae, Pasteurella multocida.*

Anaerobes: Bacteroides species* including *B. fragilis.*

* Some members of these species of bacteria produce beta-lactamase, rendering them insensitive to amoxicillin alone.

5.2 Pharmacokinetic properties

The pharmacokinetics of the two components of Augmentin are closely matched. Peak serum levels of both occur about one hour after oral administration. Absorption of Augmentin is optimised at the start of a meal. Both clavulanate and amoxicillin have low levels of serum binding; about 70% remains free in the serum.

Double the dosage of Augmentin approximately doubles the serum levels achieved.

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 250/125mg or a single 500/125mg 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 metabolised 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.

5.3 Preclinical safety data

No further information of relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Xanthan gum, (E415)
Hypromellose, (E464)
Aspartame (E951)
Silica colloidal anhydrous
Silicon Dioxide
Succinic acid
Raspberry dry flavour
Orange dry flavour 1
Orange dry flavour 2
Golden syrup dry flavour

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

Dry powder: 2 years
Reconstituted suspension according to directions: 7 days
Discard any unused suspension seven days after reconstitution.

6.4 Special precautions for storage

Dry powder: Do not store above 25ºC. Store in the original container to protect from moisture.
Reconstituted suspension according to directions: Store between 2ºC and 8ºC
Do not freeze

6.5 Nature and contents of container

Glass bottles with aluminium screw caps of a ROPP, internally lacquered closure, containing a flowed-in PVC liner containing powder for reconstitution to 100 ml.

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

At time of dispensing the dry powder should be reconstituted to for an oral suspension.

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
Stonemasons Way
Rathfarnham
Dublin 16
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 1077/93/6

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 July 1983

Date of last renewal: 28 July 2008

10 DATE OF REVISION OF THE TEXT

January 2010