IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PPA1473/015/001
Case No: 2059691

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

McDowell Pharmaceuticals

4 Altona Road, **Lisburn**, **N. Ireland**, **BT27 5QB**

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

Augmentin film-coated tablets 250mg/125mg

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 **19/06/2009**.

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 Film-coated tablets 250mg/125mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Amoxicillin trihydrate equivalent to 250 mg Amoxicillin with potassium clavulanate equivalent to 125 mg of clavulanic acid.
For a full list of excipients, see 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets
Product imported from the UK
White to off-white, oval shaped, film-coated tablets engraved 'Augmentin' on one side.

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.

Augmentin Intravenous is also indicated for Prophylaxis against wound infection which may be associated with surgical procedures such as gastrointestinal, pelvic, head and neck, cardiac, renal joint replacement and biliary tract.

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 for the treatment of infection.

Adults and Children over 12 years of age only:

The usual daily dose is 375 mg three times daily.

The dosage may be increased to 750mg three times daily in the treatment of severe infections.

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	375 -750 Depending on severity of infection	12 (b.i.d)
< 10	375 – 750 Depending on the severity of infection	24 (o.d)

Haemodialysis

Dosage adjustments are based on the maximum recommended level of Amoxicillin.

2 times 250/125mg every 24 hours PLUS one dose during dialysis, to be repeated at the end of dialysis (as serum concentrations of both Amoxicillin and clavulanic acid are decreased).

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: Tablets

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 hypersensitivity to beta-lactams e.g. penicillins or 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

Prolonged use of an anti-infective may occasionally result in overgrowth of non-susceptible organisms.

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 **Contraindications**).

'Augmentin' should be used with caution in patients with evidence of hepatic dysfunction and with care in patients with renal dysfunction.

Each tablet contains 0.63 mmol of potassium.

Patients with infectious mononucleosis frequently develop rashes with Amoxicillin therapy.

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

This product should only be used in pregnancy or lactation if considered essential by the physician. Animal studies have shown no evidence of teratogenic effect due to drug, but safety of use in human beings is not established. 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.

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 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 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).

Black hairy tongue

Hepatobiliary disorders

Uncommon A moderate rise in AST and/or ALT and Alkaline Phosphatases 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.

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 (see Overdosage)

4.9 Overdose

Gastro-intestinal 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. 'Augmentin' 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

'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 ß-lactamase enzymes, thus rendering the organisms sensitive to Amoxicillin's 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.

Doubling 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 adminstration 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 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.

5.3 Preclinical safety data

No further information of relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate
Sodium starch glycollate, Type A
Colloidal silica
Microcrystalline cellulose

Film-coat :
Titanium dioxide (E171)
Hypromellose
Macrogol
Silicone Oil

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package in order to protect from moisture. Keep blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

Aluminium/PVC/PVdC blister in an aluminium pouch with desiccant, containing 21 tablets in an over-labelled carton.

6.6 Special precautions for disposal and other handling

No special requirements

7 Parallel Product Authorisation Holder

McDowell Pharmaceuticals,
4 Altona Road,
Lisburn,
N.Ireland
BT27 5QB

8 Parallel Product Authorisation Number

PPA1473/15/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of Authorisation: 19th June 2009

10 DATE OF REVISION OF THE TEXT