

**IRISH MEDICINES BOARD ACTS 1995 AND 2006**

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

**(S.I. No.540 of 2007)**

**PA0126/103/003**

Case No: 2051983

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

**Clonmel Healthcare Limited**

**Waterford Road, Clonmel, Co. Tipperary, Ireland**

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

**CLAVAMEL 125mg/62.5mg per 5ml Junior 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 **26/06/2008** until **16/09/2009**.

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

Clavamel 125 mg/62.5 mg per 5 ml Junior 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 62.5mg of clavulaic acid.

For excipients, see 6.1.

#### 3 PHARMACEUTICAL FORM

Powder for oral suspension

Clear, glass bottles, containing a white to off-white powder for reconstitution with water.

#### 4 CLINICAL PARTICULARS

##### 4.1 Therapeutic Indications

Clavamel 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.

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

Mixed infections caused by amoxicillin-susceptible organisms in conjunction with Clavamel-susceptible beta-lactamase-producing organisms may be treated with Clavamel. 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.)
< 10	15/3.75* mg/kg (maximum 500/125mg)	24 (o.d.)

\* 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 Clavamel 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.

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

## 4.4 Special warnings and precautions for use

Before initiating therapy with 'Clavamel' 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).

'Clavamel' 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).

'Clavamel' 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 micro-organisms including candida resistant to that anti-infective.

Clavamel Suspension contains 12.5 mg aspartame per 5 ml dose and therefore care should be taken in phenylketonuria. Each 5 ml dose contains 12.3 mg (0.31 mmol) potassium.

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 clavulanate acid.

Prolongation of bleeding time and prothrombin time have been reported in some patients receiving co-amoxiclav. Augmentin-Duo 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 not 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 co-amoxiclav 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 Clavamel may be associated with an increased risk of necrotising enterocolitis in neonates. As with all other medicines use should be avoided in pregnancy unless considered essential by the physician.

Use in lactation:

'Clavamel' 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 CLAVAMEL at the start of a meal.

Uncommon Indigestion.  
 Very Rare Antibiotic-associated colitis (including pseudomembraneous colitis and haemorrhagic colitis).  
 Black hairy tongue.

#### Hepatobiliary disorders

Uncommon A moderate rise in aspartate amino transferase (AST) and/or alanine amino transferase (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

Vary 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

Clavamel 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 Clavamel anticipates this defence mechanism by blocking the beta-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 Clavamel, it produces an antibiotic agent of broad spectrum with wide application in hospital and general practice.

Clavamel 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 Clavamel are closely matched. Peak serum levels of both occur about one hour after oral administration. Absorption of Clavamel 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 Clavamel 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 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**

Xanthan gum, E415  
Hypromellose, E464  
Aspartame  
Colloidal anhydrous silica  
Colloidal hydrated silica  
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: 7 days.

### **6.4 Special precautions for storage**

Dry powder: Do not store above 25°C.  
Reconstituted suspensions should be kept in a refrigerator (but not frozen) for up to seven days.

### **6.5 Nature and contents of container**

Glass bottles with aluminium screw caps or a ROPP (roll on pilfer proof), internally lacquered externally enameled closure, containing a flowed-in PVC liner. Containing powder for reconstitution to 100ml.

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**

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

## **7 MARKETING AUTHORISATION HOLDER**

Clonmel Healthcare Ltd  
Waterford Road  
Clonmel  
Co Tipperary

**8 MARKETING AUTHORISATION NUMBER**

PA 126/103/3

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 17 September 1999

Date of last renewal: 17 September 2004

**10 DATE OF REVISION OF THE TEXT**

June 2008