Public Assessment Report

Decentralised Procedure

CO-AMOXICLAV 500/125MG FILM-COATED TABLETS
CO-AMOXICLAV 875/125MG FILM-COATED TABLETS

Procedure No: UK/H/1333/002-3/DC

UK Licence No: PL 31774/0002-3

BLUEFISH PHARMACEUTICALS AB
LAY SUMMARY

On 7th September 2009, the MHRA granted Bluefish Pharmaceuticals AB Marketing Authorisations (licences) for the medicinal products Co-amoxiclav 500/125mg and 875/125mg Film-coated Tablets (PL 31774/0002-3). These are prescription-only medicines (POM) that are used as broad spectrum antibiotics for treating a wide range of bacterial infections. They belong to a group of antibiotics called “penicillins”.

The active ingredients are amoxicillin and clavulanic acid. Amoxicillin works by killing the bacteria that can cause infections and clavulanic acid protects amoxicillin from bacterial degradation.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Co-amoxiclav 500/125mg and 875/125mg Film-coated Tablets outweigh the risks, hence Marketing Authorisations have been granted.
TABLE OF CONTENTS

Module 1: Information about initial procedure Page 3
Module 2: Summary of Product Characteristics Page 4
Module 3: Product Information Leaflets Page 22
Module 4: Labelling Page 24
Module 5: Scientific Discussion Page 28

1 Introduction
2 Quality aspects
3 Non-clinical aspects
4 Clinical aspects
5 Overall conclusions

Module 6 Steps taken after initial procedure
### Module 1

| **Product Name** | Co-Amoxiclav 500/125mg Film-Coated Tablets  
Co-Amoxiclav 875/125mg Film-Coated Tablets |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substances</strong></td>
<td>Amoxicillin trihydrate, potassium clavulanate</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Film-coated tablet</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>500mg or 875mg amoxicillin trihydrate, and 125mg potassium clavulanate</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Bluefish Pharmaceuticals AB, Torsgatan 11, 111 23 Stockholm, Sweden</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>CMS</strong></td>
<td>Czech Republic, Germany, Hungary, Ireland, Italy, Poland, Slovenia and Spain</td>
</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/1333/002-3/DC</td>
</tr>
<tr>
<td><strong>Timetable</strong></td>
<td>Day 210 – 20th May 2009</td>
</tr>
</tbody>
</table>
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Co-amoxiclav 500 mg/125 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film coated tablet contains 575.0 mg amoxicillin trihydrate equivalent to 500 mg amoxicillin and potassium clavulanate equivalent to 125 mg clavulanic acid.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film coated tablet.
White to off white oval film coated tablet.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Amoxicillin-clavulanate is indicated for the treatment of the following bacterial infections when amoxicillin resistant β-lactamase-producing strains are suspected as the cause (see section 5.1). In other situations, amoxicillin alone should be considered:
• Upper respiratory tract infections (including ENT): recurrent tonsillitis, acute sinusitis, acute otitis media;
• Lower respiratory tract infections: acute exacerbations of chronic bronchitis, community-acquired pneumonia;
• Urinary tract infections: cystitis (especially when recurrent or complicated – excluding prostatitis), pyelonephritis;
• Skin and soft tissue infections: cellulitis, animal bites and severe dental abscess with spreading cellulitis;
• Other infections: septic abortion, puerperal sepsis, intra-abdominal sepsis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration
Route of administration: oral use

Co-amoxiclav is not recommended for use in children below 12 years of age due to a lack of data on safety and efficacy.

Dosage depends on the age, weight and renal function of the patient and the severity of the infection. Dosages are expressed throughout in terms of amoxicillin-/clavulanate content except when doses are stated in terms of an individual component.

To minimise potential gastrointestinal intolerance, administer at the start of a meal. The absorption of amoxicillin-clavulanate is optimised when taken at the start of a meal.

Treatment should not be extended beyond 14 days without review. Therapy can be started parenterally and continued with an oral preparation

Usual dosage of amoxicillin-clavulanate in adults and adolescents ≥ 40 kg is one 500 mg/125 mg tablet taken two times a day.

Usual dosages for the treatment of severe infections is one 500/125 mg tablet taken three times a day.

More suitable paediatric formulations of amoxicillin-clavulanate are available for the treatment in children.

Elderly
No adjustment needed; dose as for adults. If there is evidence of renal impairment, dose should be adjusted as for renally impaired adults.
Renal impairment
In patients with moderate or severe renal impairment, dosages should be adjusted according to the degree of impairment

Dosage adjustments are based on the maximum recommended level of amoxicillin

| Creatinine clearance greater than 30 ml/min | No adjustment necessary. |
| Creatinine clearance 10 to 30 ml/min | One 500/125 mg tablet twice daily. |
| Creatinine clearance less than 10 ml /min | Not recommended |

Haemodialysis
One 500/125 mg tablet every 24 h, PLUS one 500/125 mg tablet 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 insufficient data on which to base a dosage recommendation.

4.3 Contraindications
Amoxicillin-clavulanate is contraindicated:
- in patients with a history of hypersensitivity to beta-lactams, e.g. penicillins and cephalosporins and to any of the excipients.
- in patients with a previous history of amoxicillin-clavulanate-associated jaundice/hepatic dysfunction.

4.4 Special warnings and precautions for use
Prolonged use may also occasionally result in overgrowth of non-susceptible organisms.

Before initiating therapy with amoxicillin-clavulanate, 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 (see contraindications).

Change in liver function tests have been observed in some patients receiving co-amoxiclav. The clinical significance of these changes is uncertain but co-amoxiclav should be used with caution in patients with evidence of hepatic dysfunction.

Cholestatic jaundice, which may be severe, but is usually reversible, has been reported rarely. Signs and symptoms may not become apparent for several weeks after treatment has ceased.

In patients with renal impairment, dosage should be adjusted according to the degree of impairment (see Dosage and Administration– Renal impairment).

Co-amoxiclav 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.

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

Each Co-amoxiclav 500 mg/125 mg Film- coated Tablets contains 25 mg (i.e. 0.64 mmol) of potassium.
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 Co-amoxiclav. Co-amoxiclav 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.

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.

Co-amoxiclav 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**

Co-amoxiclav has no influence on the ability to drive and use machines.

4.8 **Undesirable effects**

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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.
- **Not known** (cannot be estimated from the available data).

**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)

**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
- 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 section 4.9)

4.9 Overdose
Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. GI symptoms may be treated symptomatically, with attention to the water/electrolyte balance. Co-amoxiclav can 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: β-lactam antibacterials, combination of penicillin and beta-lactamase inhibitor ATC code: JOICR02

Mode of action
Amoxicillin is a semisynthetic penicillin that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall that is usually followed by cell lysis and bacterial death.

Clavulanic acid is a beta-lactam agent structurally related to penicillins that can inactivate certain (but not all) beta-lactamase enzymes manufactured by bacteria and so can prevent enzymic degradation of amoxicillin.

Pharmacokinetic/Pharmacodynamic Relationship
The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for beta-lactam agents.

Mechanisms of resistance
There are two main mechanisms of resistance to beta-lactam antibiotics, i.e. target (PBP) alteration and inactivation by beta-lactamases. Less often impermeability or efflux pump mechanisms may cause or contribute to bacterial resistance.

Breakpoints
MIC breakpoints for co-amoxiclav shown below are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) except for Staphylococci, for which there are no
EUCAST MIC breakpoints and therefore those recommended by the Clinical and Laboratory Standards Institute (CLSI; 2008) are given.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Susceptibility Breakpoints (μg/ml)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Susceptible</td>
<td>Intermediate</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em>³</td>
<td>≤ 0.5</td>
<td>1-2</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>≤ 1</td>
<td>-</td>
</tr>
<tr>
<td>*Staphylococcus spp.*⁴</td>
<td>≤ 4</td>
<td>-</td>
</tr>
<tr>
<td>Enterobacteriaceae⁵</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

1 The reported values are for Amoxicillin concentrations. For susceptibility testing purposes, the concentration of clavulanic acid is fixed at 2 mg/l

3 Breakpoint values in the table are based on ampicillin breakpoints.

4 CLSI breakpoints (no intermediate value is specified). Staphylococci which are susceptible to amoxicillin/clavulanic acid but resistant to methicillin/oxacillin must be considered as resistant.

5 The resistant breakpoint of R>8 mg/L ensures that all isolates with resistance mechanisms are reported resistant.

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. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Co-amoxiclav is bactericidal to a wide range of organisms including:

**Gram-positive aerobes:**
- *Bacillus anthracis*#
- *Corynebacterium* species
- *Enterococcus faecalis*#
- *Enterococcus faecium*#
- *Listeria monocytogenes*
- *Nocardia asteroides*
- *Staphylococcus aureus*#
- Coagulase negative *staphylococci*# (including *Staphylococcus epidermidis*#)
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*
- *Streptococcus species*
- *Streptococcus viridans*

**Gram-negative aerobes:**
- *Bordetella pertussis*
- *Brucella* species
- *Escherichia coli*#
- *Gardnerella vaginalis*
- *Haemophilus influenzae*#*Helicobacter pylori*
- *Klebsiella* species#
- *Legionella* species
- *Moraxella catarrhalis*# (Branhamella catarrhalis)
- *Neisseria gonorrhoeae*#
- *Neisseria meningitidis*#
- *Pasteurella multocida*
- *Proteus mirabilis*#
- *Proteus vulgaris*#
- *Salmonella* species#
- *Shigella* species#
- *Vibrio cholerae*
- *Yersinia enterocolitica*#
**Gram-positive anaerobes:**
- Clostridium species
- Peptococcus species
- Peptostreptococcus species

**Gram-negative anaerobes:**
- Bacteroides species# (including Bacteroides fragilis)
- Fusobacterium species#

**Others:**
- Borrelia burgdorferi
- Chlamydiae
- Leptospira icterohaemorrhagiae
- Treponema pallidum

**Species for which acquired resistance may be a problem:**

<table>
<thead>
<tr>
<th>Gram-positive aerobes:</th>
<th>Enterococcus faecium#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-negative aerobes:</td>
<td>Escherichia coli#</td>
</tr>
<tr>
<td></td>
<td>Klebsiella sp.#</td>
</tr>
<tr>
<td></td>
<td>Shigella sp.#</td>
</tr>
<tr>
<td></td>
<td>Salmonella sp.#</td>
</tr>
<tr>
<td></td>
<td>Yersinia enterocolitica#</td>
</tr>
</tbody>
</table>

**Inherently resistant organisms:**

<table>
<thead>
<tr>
<th>Gram-positive aerobes:</th>
<th>Methicillin-resistant staphylococci (MRSA/MRSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-negative aerobes:</td>
<td>Pseudomonas sp.</td>
</tr>
<tr>
<td></td>
<td>Stenotrophomonas maltophilia</td>
</tr>
<tr>
<td></td>
<td>Acinetobacter spp.</td>
</tr>
<tr>
<td></td>
<td>Serratia spp.</td>
</tr>
</tbody>
</table>

# Some members of these species of bacteria produce beta-lactamase and are therefore insensitive to amoxicillin alone.

### 5.2 Pharmacokinetic properties

**Absorption**
The two components, of amoxicillin-clavulanate, 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 amoxicillin-clavulanate is optimised when taken at the start of a meal.

**Distribution**
Following i.v. 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.

Co-amoxiclav, 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.
Metabolism
Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to 10 to 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.

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 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of a single 250/125 mg or a single 500/125 mg tablet.

Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (see Interactions).

5.3 Preclinical safety data
Nonclinical data reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity and toxicity to reproduction. Carcinogenicity studies have not been conducted with Augmentin or its components. However, potassium clavulanate alone or combined 1:2 or 1:4 with amoxicillin has been tested in a comprehensive battery of in vitro and in vivo genotoxicity tests which showed no significant genotoxic hazard.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Core tablet-
Microcrystalline Cellulose (AVICEL Ph 102)
Crucarmellose sodium
Purified Talc
Magnesium Stearate

Coating -
Hypromellose (E-15)
Ethylcellulose
Propylene Glycol
Hydroxy propyl cellulose
Titanium dioxide

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
18 months

6.4 Special precautions for storage
Do not store above 25°C.

6.5 Nature and contents of container
The tablets are available in blisters and are sealed in aluminium pouches. 7, 10, 12, 14, 20, 21 & 24 film-coated tablets in PVC/Al blister packs. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Bluefish Pharmaceuticals AB
Torsgatan 11, 111 23 Stockholm
Sweden

8 MARKETING AUTHORISATION NUMBER(S)
PL 31774/0002
9  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   07/09/2009

10  DATE OF REVISION OF THE TEXT
    07/09/2009
1 **NAME OF THE MEDICINAL PRODUCT**
Co-amoxiclav 875 mg/125 mg Film-coated Tablets

2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each film coated tablet contains 1006.25 mg amoxicillin trihydrate equivalent to 875 mg amoxicillin and potassium clavulanate equivalent to 125 mg clavulanic acid.

For a full list of excipients, see section 6.1.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide in to equal doses.

3 **PHARMACEUTICAL FORM**
Film coated tablet.
White to off white oval-shaped film-coated tablet with breakline on both sides.

4 **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**
Amoxicillin-clavulanate is indicated for the treatment of the following bacterial infections when amoxicillin resistant β-lactamase-producing strains are suspected as the cause (see section 5.1). In other situations, amoxicillin alone should be considered:

- Upper respiratory tract infections (including ENT): recurrent tonsillitis, acute sinusitis, acute otitis media;
- Lower respiratory tract infections: acute bacterial exacerbations of chronic bronchitis, community-acquired pneumonia;
- Urinary tract infections: cystitis (especially when recurrent or complicated – excluding prostatitis), pyelonephritis;
- Skin and soft tissue infections: cellulitis, animal bites and severe dental abscess with spreading cellulitis;
- Other infections: septic abortion, puerperal sepsis, intra-abdominal sepsis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 **Posology and method of administration**
Route of administration: oral use

Co-amoxiclav is not recommended for use in children below 12 years of age due to a lack of data on safety or efficacy.

Dosage depends on the age, weight and renal function of the patient and the severity of the infection. Dosages are expressed throughout in terms of amoxicillin-/clavulanate content except when doses are stated in terms of an individual component.

To minimise potential gastrointestinal intolerance, administer at the start of a meal. The absorption of amoxicillin-clavulanate is optimised when taken at the start of a meal.

Treatment should not be extended beyond 14 days without review. Therapy can be started parenterally and continued with an oral preparation

**Usual dosages for the treatment of infection: Adults and children over 12 years of age only**

| Severe infections | 875 mg /125 mg given twice daily |

More suitable paediatric formulations of amoxicillin-clavulanate are available for the treatment in children.

**Elderly**
No adjustment needed; dose as for adults. If there is evidence of renal impairment, dose should be adjusted as for renally impaired adults.

**Renal impairment**
No dose adjustment is needed when creatinine clearance is >30 ml/min. In patients with renal impairment (creatinine clearance <30 ml/min) and on haemodialysis, the 875 mg /125 mg tablets
should not be used. Dose adjustment is needed in these patients and more suitable formulations are available.

**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 is contraindicated:
- in patients with a history of hypersensitivity to beta-lactams, e.g. penicillins and cephalosporins and to any of the excipients.
- in patients with a previous history of amoxicillin-clavulanate-associated jaundice/hepatic dysfunction.

4.4 **Special warnings and precautions for use**
Prolonged use may also occasionally result in overgrowth of non-susceptible organisms.

Before initiating therapy with amoxicillin-clavulanate, 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 (see contraindications).

Change in liver function tests have been observed in some patients receiving co-amoxiclav. The clinical significance of these changes is uncertain but co-amoxiclav should be used with caution in patients with evidence of hepatic dysfunction.

Cholestatic jaundice, which may be severe, but is usually reversible, has been reported rarely. Signs and symptoms may not become apparent for several weeks after treatment has ceased.

In patients with renal impairment, dosage should be adjusted according to the degree of impairment (see Dosage and Administration– Renal impairment).

Co-amoxiclav 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.

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

Each Co-amoxiclav 875 mg/125 mg Film- coated Tablets contains 25 mg (i.e. 0.64 mmol) of potassium.

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 Co-amoxiclav. Co-amoxiclav 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.

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.

Co-amoxiclav 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
Co-amoxiclav has no influence on the ability to drive and use machines.

4.8 Undesirable effects
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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 \( \geq \frac{1}{10} \)
common \( \geq \frac{1}{100} \) and <\( \frac{1}{10} \)
uncommon \( \geq \frac{1}{1000} \) and <\( \frac{1}{100} \)
rare \( \geq \frac{1}{10,000} \) and <\( \frac{1}{1000} \)
very rare <\( \frac{1}{10,000} \).
Not known (cannot be estimated from the available data).

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)

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
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 section 4.9)

4.9 **Overdose**
Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. GI symptoms may be treated symptomatically, with attention to the water/electrolyte balance. Co-amoxiclav can 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: β-lactam antibacterials, combination of penicillin and beta-lactamase inhibitor ATC code: JOICR02

**Mode of action**
Amoxicillin is a semisynthetic penicillin that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall that is usually followed by cell lysis and bacterial death.

Clavulanic acid is a beta-lactam agent structurally related to penicillins that can inactivate certain (but not all) beta-lactamase enzymes manufactured by bacteria and so can prevent enzymic degradation of amoxicillin.

**Pharmacokinetic/Pharmacodynamic Relationship**
The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for beta-lactam agents.

**Mechanisms of resistance**
There are two main mechanisms of resistance to beta-lactam antibiotics, i.e. target (PBP) alteration and inactivation by beta-lactamases. Less often impermeability or efflux pump mechanisms may cause or contribute to bacterial resistance.

**Breakpoints**
MIC breakpoints for co-amoxiclav shown below are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) except for Staphylococci, for which there are no EUCAST MIC breakpoints and therefore those recommended by the Clinical and Laboratory Standards Institute (CLSI; 2008) are given.
<table>
<thead>
<tr>
<th>Organism</th>
<th>Susceptibility Breakpoints (μg/ml)</th>
<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Susceptible</td>
<td>Intermediate</td>
<td>Resistant</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em>³</td>
<td>≤ 0.5</td>
<td>1-2</td>
<td>&gt; 2</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>≤ 1</td>
<td>-</td>
<td>&gt; 1</td>
</tr>
<tr>
<td>*Staphylococcus spp.*⁴</td>
<td>≤ 4</td>
<td>-</td>
<td>≥ 8</td>
</tr>
<tr>
<td><em>Enterobacteriaceae</em>⁵</td>
<td>-</td>
<td>-</td>
<td>&gt; 8</td>
</tr>
</tbody>
</table>

1 The reported values are for Amoxicillin concentrations. For susceptibility testing purposes, the concentration of clavulanic acid is fixed at 2 mg/l

3 Breakpoint values in the table are based on ampicillin breakpoints.

4 CLSI breakpoints (no intermediate value is specified). Staphylococci which are susceptible to amoxicillin/clavulanic acid but resistant to methicillin/oxacillin must be considered as resistant.

5 The resistant breakpoint of R>8 mg/L ensures that all isolates with resistance mechanisms are reported resistant.

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. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Co-amoxiclav is bactericidal to a wide range of organisms including:

**Gram-positive aerobes:**
- *Bacillus anthracis*#
- *Corynebacterium* species
- *Enterococcus faecalis*#
- *Enterococcus faecium*#
- *Listeria monocytogenes*
- *Nocardia asteroides*
- *Staphylococcus aureus*#
- *Coagulase negative staphylococci*# (including *Staphylococcus epidermidis*#)
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*
- *Streptococcus species*
- *Streptococcus viridans*

**Gram-negative aerobes:**
- *Bordetella pertussis*
- *Brucella* species
- *Escherichia coli*#
- *Gardnerella vaginalis*
- *Haemophilus influenzae*#*Helicobacter pylori*
- *Klebsiella* species#
- *Legionella* species
- *Moraxella catarrhalis*# (*Branhamella catarrhalis*)
- *Neisseria gonorrhoeae*#
- *Neisseria meningitidis*#
- *Pasteurella multocida*
- *Proteus mirabilis*#
- *Proteus vulgaris*#
- *Salmonella* species#
- *Shigella* species#
- *Vibrio cholerae*
- *Yersinia enterocolitica*#
Gram-positive anaerobes:
- Clostridium species
- Peptococcus species
- Peptostreptococcus species

Gram-negative anaerobes:
- Bacteroides species# (including Bacteroides fragilis)
- Fusobacterium species#

Others:
- Borrelia burgdorferi
- Chlamydiaceae
- Leptospira icterohaemorrhagiae
- Treponema pallidum

**Species for which acquired resistance may be a problem:**

<table>
<thead>
<tr>
<th>Gram-positive aerobes:</th>
<th>Enterococcus faecium#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-negative aerobes:</td>
<td>Escherichia coli#</td>
</tr>
<tr>
<td></td>
<td>Klebsiella sp.#</td>
</tr>
<tr>
<td></td>
<td>Shigella sp.#</td>
</tr>
<tr>
<td></td>
<td>Salmonella sp.#</td>
</tr>
<tr>
<td></td>
<td>Yersinia enterocolitica#</td>
</tr>
</tbody>
</table>

**Inherently resistant organisms:**

<table>
<thead>
<tr>
<th>Gram-positive aerobes:</th>
<th>Methicillin-resistant staphylococci (MRSA/MRSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-negative aerobes:</td>
<td>Pseudomonas sp.</td>
</tr>
<tr>
<td></td>
<td>Stenotrophomonas maltophilia</td>
</tr>
<tr>
<td></td>
<td>Acinetobacter spp.</td>
</tr>
<tr>
<td></td>
<td>Serratia spp.</td>
</tr>
</tbody>
</table>

# Some members of these species of bacteria produce beta-lactamase and are therefore insensitive to amoxicillin alone.

5.2 Pharmacokinetic properties

**Absorption**
The two components, of amoxicillin-clavulanate, 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 amoxicillin-clavulanate is optimised when taken at the start of a meal.

**Distribution**
Following i.v. 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.

Co-amoxiclav, 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.
Metabolism
Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to 10 to 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.

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 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of a single 250/125 mg or a single 500/125 mg tablet.

Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (see Interactions).

5.3 Preclinical safety data
Nonclinical data reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity and toxicity to reproduction. Carcinogenicity studies have not been conducted with Augmentin or its components. However, potassium clavulanate alone or combined 1:2 or 1:4 with amoxicillin has been tested in a comprehensive battery of in vitro and in vivo genotoxicity tests which showed no significant genotoxic hazard.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Core tablet-
- Microcrystalline Cellulose (AVICEL Ph 102)
- Croscarmellose sodium
- Purified Talc
- Magnesium Stearate

Coating -
- Hypromellose (E-15)
- Ethylcellulose
- Propylene Glycol

- Hydroxy propyl cellulose
- Titanium dioxide

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
18 months

6.4 Special precautions for storage
Do not store above 25°C.

6.5 Nature and contents of container
The tablets are available in blisters and are sealed in aluminium pouches.
- 7, 10, 12, 14, 20, 21 & 24 film-coated tablets in PVC/Al blister packs.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Bluefish Pharmaceuticals AB
Torsgatan 11, 111 23 Stockholm
Sweden

8 MARKETING AUTHORISATION NUMBER(S)
PL 31774/0003
DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
07/09/2009

DATE OF REVISION OF THE TEXT
07/09/2009
Co-amoxiclav 500 mg/125 mg film-coated tablets
(Amoxicillin and clavulanic acid)

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

In this leaflet:
1. What Co-amoxiclav is and what it is used for
2. Before you take Co-amoxiclav
3. How to take Co-amoxiclav
4. Possible side effects
5. How to store Co-amoxiclav
6. Further information

1. WHAT CO-AMOXICLAV IS AND WHAT IT IS USED FOR

Co-amoxiclav is a broad spectrum antibiotic used for treating a wide range of bacterial infections. It belongs to a group of medicines called "beta-lactam". It contains two active ingredients: amoxicillin and clavulanate potassium.

2. BEFORE YOU TAKE CO-AMOXICLAV

If you have any of the following conditions or are unsure as to whether or not you should be taking Co-amoxiclav talk to your doctor or pharmacist.

Do not take Co-amoxiclav:
- if you are allergic (hypersensitive) to amoxicillin, clavulanate potassium or any of the ingredients of the medicinal product. Check the ingredients listed in Section 6.
- if you have ever had a skin rash or swelling of the face or neck when taking any antibiotic.
- if you know you are allergic to penicillin or any other antibiotic.
- if the patient is under 12 years old.
- if you have ever had penicillin allergy before taking an antibiotic.

Take special care with Co-amoxiclav:
- if you are taking a contraceptive pill (in which case you will need to take extra contraceptive precautions such as using a condom).
- if you suffer from kidney or liver problems or have glomerulonephritis if you are suffering from diarrhoea or vomiting.

Taking other medicines
If you are taking other medicines, including those bought without prescription, in particular, please tell your doctor if you are taking any of the following in addition to Co-amoxiclav:
- warfarin, or any other medicine, used to prevent blood clots (anticoagulants).
- medicines to treat liver or kidney problems.
- aspirin, to treat your pain, or any other medicine that may increase the risk of skin reactions.
- medicines used to treat gout, or any other medicine that may increase the risk of skin reactions.
- any medicine that could cause damage to the kidneys.

Tobacco and smoking
Co-amoxiclav should be taken just before meals and oralized whole with water. Do not chew them.

Pregnancy and breastfeeding
Inform your doctor if you are pregnant, planning to become pregnant or if you are breast-feeding. Co-amoxiclav should not be used when pregnant or breast-feeding unless your doctor decides that the benefits outweigh the risks.

Driving and using machines
Co-amoxiclav Tablets have no known effect on the ability to drive and use machines. However, if you experience any side effects such as dizziness, your ability to drive or operate machines may be impaired. Important information about one of the ingredients of Co-amoxiclav:
Each Co-amoxiclav 500 mg/125 mg Film-coated Tablets contains 25 mg (i.e. 5.64 amol) of potassium.

3. HOW TO TAKE CO-AMOXICLAV

Always take Co-amoxiclav exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

- These tablets are usually prescribed for adults and children over 12 years old and with the body weight of at least 40 kg.
- The usual dose is one 500/125 mg Tablet taken two times a day.
- The usual dose for the treatment of certain infections is one 500/125 mg Tablet taken three times a day.
- Your doctor will prescribe the exact dosage.
- Never take more than the recommended daily dose.
- Co-amoxiclav should be swallowed whole with water - do not chew them.
- For the best results, take Co-amoxiclav just before meals.
- If you still feel unwell after finishing the treatment, go and see your doctor again.
- You should not use Co-amoxiclav by the end of two weeks without seeing your doctor again.

Children
Co-amoxiclav is not recommended for use in children of 12 years and under.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Co-amoxiclav can cause side effects, although not everybody will experience them.

If you experience any of the following side effects, stop taking Co-amoxiclav and seek immediate medical attention:
- skin rash, itching, or swelling of the face, lips, tongue, or throat, or breathing problems.
- swelling of the face, lips, tongue, or throat, or breathing problems.
- swelling, redness or heat, or loss of consciousness.
- dizziness, drowsiness, headache.
- raised liver enzymes on blood test results.

Very rare (occurs in less than 1 in 10,000 patients):
- hypersensitivity or anaphylaxis (these reactions are severe).
- inflammation of the liver: either acute (usually only visible under a microscope) which may be accompanied by cloudy urine or by difficulty in passing in passing urine. You should drink plenty of fluids (such as water and non-alcoholic and non-coffee-containing drinks) to reduce the risk of these reactions.

Some of these reactions can be delayed for several weeks after finishing the treatment.

If you are having blood test, tell your doctor you are taking Co-amoxiclav. This is because this medicated product sometimes causes short-term changes in blood cell counts.

If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

5. HOW TO STORE CO-AMOXICLAV

Do not store above 25°C.

Keep out of reach of children.

Do not take your tablets after the expiry date printed on the package. The expiry date refers to the last day of that month.

Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Co-amoxiclav Tablets contain:
The active substances are amoxicillin and clavulanic acid.

Other ingredients include:
- sorbitol (E420), xanthan gum (E415), sodium benzoate (E211), sodium carbonate, tricalcium phosphate, crospovidone, hydroxypropyl cellulose, magnesium stearate and polyethylene glycol 6000.

What Co-amoxiclav looks like and contents of the pack:
Co-amoxiclav 500 mg/125 mg Tablets are white to off-white, film-coated, oval-shaped tablets which are supplied in Pvc-Aluminium blisters packs of 21 (5.512.5), 24, 30, 31 and 34 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Bluefish Pharmaceuticals AB, Torsgatan 11 SE-111 21 Stockholm, Sweden. Tel: +46 80181600

This medicinal product is authorised in the Member States of the EEA under the following names:

Czech Republic: Co-amoxiclav 500 mg/125 mg Film-Coated Tablets
Germany: Co-amoxiclav 500 mg/125 mg Film-Coated Tablets
Hungary: Co-amoxiclav 500 mg/125 mg Film Coated Tablets
Ireland: Co-amoxiclav 500 mg/125 mg Film Coated Tablets
Italy: Amoxicillin a soluzione abbreviata Tablets 500 mg/125 mg
Poland: Co-amoxiclav 500 mg/125 mg Film-Coated Tablets
Slovenia: Amoxicillin / clavulanát 500 mg/125 mg tablets film-coated tablets
Spain: Co-amoxiclav 500 mg/125 mg Film-Coated Tablets
United Kingdom: Co-amoxiclav 500 mg/125 mg Film-Coated Tablets

21
PAR Co-Amoxiclav 500/125 and 875/125mg Film-Coated Tablets

UK/H/1333/002-3/DC

PACKAGE LEAFLET: INFORMATION FOR THE USER

Co-amoxiclav 875 mg / 125 mg film-coated tablets

(Amoxicillin and clavulanic acid)

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them.
- Even if these symptoms are the same as yours.
- If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please see your doctor or pharmacist.

1. WHAT Co-amoxiclav is and what is it used for

Co-amoxiclav is a broad-spectrum antibiotic, used for treating a wide range of bacterial infections. It belongs to a group of antibiotics called "penicillins". It contains two active ingredients: amoxicillin and clavulanic acid.

Amoxicillin works by killing the bacteria that cause infections, and clavulanic acid protects amoxicillin from bacterial degradation.

2. BEFORE YOU TAKE Co-amoxiclav

If you have any of the below conditions you are unsure of or whatever you are taking you should be taking Co-amoxiclav tablets in your doctor or pharmacist.

Do not take Co-amoxiclav:
- if you have allergic (hypersensitivity) to amoxicillin, clavulanic acid or any of the ingredients of the medicinal product.
- if you have had a skin rash or swelling of the face or neck when taking any antibiotics.
- if you are allergic to penicillins (or any other antibiotics).
- if you are pregnant or breast feeding.
- if you have ever had problems in getting an antibiotic.

Taking special care with Co-amoxiclav:
- if you are taking a contraceptive pill (in which case you will need to take extra contraceptive measures such as using condoms).
- if you suffer from kidney or liver problems if you have glaucoma (or if you are suffering from diarrhea or vomiting).

Taking other medicines

Please tell your doctor or pharmacist if you are taking, or have recently taken, any other medicines, including over-the-counter medicines without a prescription. In particular, please tell your doctor if you are taking any of the following Co-amoxiclav may interact with these over-the-counter medicines:
- warfarin, or any other medicine, used to prevent blood clot (anticoagulants)
- medicines to treat liver or kidney problems.
- antidepressants, to treat depression, or any that increase the risk of skin reactions.
- propranolol, also used to treat heart, since this can cause the increased levels of amoxicillin in the blood.
- oral contraceptives.

Taking Co-amoxiclav with food and drink

Co-amoxiclav should be taken just before meals and continued whole with water. Do not chew them.

Food and lifestyle:

Inform your doctor if you are pregnant, planning to become pregnant or if you are breast-feeding.

Co-amoxiclav should not be used while pregnant or breast-feeding unless your doctor decides that the benefits outweigh the risks.

Driving and using machines:

Co-amoxiclav tablets have no known effect on the ability to drive and use machines. However, if you experience any side effects such as dizziness, you utility to drive or operate machines may be impaired.

Important information about the ingredients of Co-amoxiclav:

Each Co-amoxiclav 875/125 mg Film-coated Tablets contains 25 mg (i.e. 0.64 molecule) of potassium.

3. HOW TO TAKE Co-amoxiclav

Always take Co-amoxiclav exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

- These tablets are usually prescribed for adults and children over 13 years old and with the body weight of at least 50 kg.
- The usual dose is one 875 mg / 125 mg tablet, taken twice a day.
- Your doctor will prescribe the exact dosage.
- Never take more than the recommended daily dose.
- Co-amoxiclav should be swallowed whole without water – do not chew them.
- For the best results, take Co-amoxiclav in the same food.
- If you still feel unwell after finishing the treatment, go and see your doctor again.
- You should not use Co-amoxiclav beyond four weeks without seeing your doctor again.

Children

Co-amoxiclav is not recommended for use in children under 12 years of age.

Kidney and Liver problems:
- If you have kidney problems the dose might be changed.
- If you have liver problems you may have more frequent blood tests to see how your liver is working.

If you take more Co-amoxiclav than you should:
- If you or someone else accidentally takes too many Co-amoxiclav Tablets, contact your doctor or nearest emergency department immediately. Show the doctor your pack of tablets.

If you forget to take Co-amoxiclav:
- If you forget to take a tablet, take it as soon as you remember. Then carry on as before. Try not to miss more than 1 dose. Do not take 2 doses within 1 hour of each other.

If you stop taking Co-amoxiclav:

Finish the full course prescribed by your doctor even if you feel better. If you stop treatment too early, recurrence or re-infection is possible.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Co-amoxiclav can cause side effects, although not everybody will experience them.

If you experience any of the following side effects, stop taking Co-amoxiclav Tablets and seek immediate medical attention:

- Loss of appetite or nausea.
- Digging or feeling sick in the stomach.
- Loss of taste.
- Diarrhoea.
- Infection of the eyes, nose, throat or skin.
- Enlargement of the liver in adults.

Suspicion, swelling of the larynx, pharynx or tongue.

Some or all of these symptoms are reversible.

Common (occur in less than 1 in 10 but more than 1 in 100 people):
- Skin rashes or itching (these symptoms are reversible).
- Nausea, vomiting or diarrhoea.
- Enlargement of the liver in adults.
- Pain in the joints.

If you feel any of these symptoms or experience any of the above symptoms, you should seek medical attention immediately.

Some symptoms such as liver enlargement may require hospitalisation.

5. HOW TO STORE Co-amoxiclav

Do not store above 25°C.

Keep out of reach of children.

Do not take your tablets after the expiry date printed on the package. The expiry date refers to the last day of that month.

Medicines should not be disposed of in the household or landfills. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Co-amoxiclav Tablets contain:

The active substances are amoxicillin and clavulanic acid.

The other ingredients are microcrystalline cellulose (E100), MCC, microcrystalline cellulose, croscarmellose sodium, pregelatinised starch, magnesium stearate, dimethyl silicone, talc, red iron oxide, titanium dioxide, and talc (colours and flavors are added).

What Co-amoxiclav looks like and contains of the pack:

Co-amoxiclav 875 mg / 125 mg Tablets are white to off-white, oval-shaped tablets which are applied as a blister pack of 7, 10, 12, 14, 20, 21 and 28 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer:

Bluefish Pharmaceuticals AB, Träskagatan 11, S-113 13 Stockholm, Sweden. Tel: +46 8 769 00 70

This leaflet was last printed in 2022.

This medicinal product is authorized in the Member States of the EEA under the following names:

Czech Republic:
- Co-amoxiclav Tablets 875 mg / 125 mg Film-Coated Tablets

Germany:
- Co-amoxiclav Tablets 875 mg /125 mg Film-Coated Tablets

Hungary:
- Co-amoxiclav Tablets 875 mg / 125 mg Film-Coated Tablets

Ireland:
- Co-amoxiclav Tablets 875 mg / 125 mg Film-Coated Tablets

Israel:
- Co-amoxiclav Tablets

Norway:
- Macromedica b.v.

Slovakia:
- Co-amoxiclav Tablets 875 mg / 125 mg Film-Coated Tablets

United Kingdom:
- Co-amoxiclav Tablets 875 mg / 125 mg Film-Coated Tablets

22
Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the applications for Co-amoxiclav 500/125mg and 875/125mg Film-coated Tablets (PL 31774/0002-3; UK/H/1333/002-3/DC) could be approved. The products are prescription-only medicines for the treatment of the following bacterial infections when amoxicillin resistant β-lactamase-producing strains are suspected as the cause.

These are applications made under the decentralised procedure (DCP), according to Article 10.1 of 2001/83 EC, as amended, claiming to be generic medicinal products of Augmentin 625mg and 1g Film-coated Tablets, which were originally granted in 1991 and 1993, respectively. The current marketing authorisation holder is Glaxo SmithKline.

Amoxicillin is a member of the penicillin family. The penicillin nucleus consists of a thiazolidine ring connected to a β-lactam ring to which is attached a side-chain. The side-chain determines most of the pharmacological and antibacterial properties of the penicillin in question. In the case of amoxicillin the benzyl ring in the side chain extends the range of antimicrobial activity into the Gram-negative bacteria. Amoxicillin kills bacteria by interfering with the synthesis of the bacterial cell wall. As a result the bacterial cell wall is weakened, the cell swells and then ruptures. Amoxicillin is readily hydrolysed by the staphylococcal penicillinase. Its spectrum of activity is extended by administration with the β-lactamase inhibitor clavulanic acid. Clavulanate by itself has little antibacterial activity.

No new preclinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of these products.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Co-amoxiclav 500/125mg Film-coated Tablets  
Co-amoxiclav 875/125mg Film-coated Tablets |
|-------------------------------------------------|----------------------------------------------------------------------------------|
| Name(s) of the active substance(s) (INN)         | Amoxicillin trigydrate  
Potassium clavulanate |
| Pharmacotherapeutic classification (ATC code)    | Beta-lactam antibacterials, penicillin (J01C R02) |
| Pharmaceutical form and strength(s)             | 500/125mg Film-Coated Tablets  
875/125mg Film-Coated Tablets |
| Reference numbers for the Mutual Recognition Procedure | UK/H/1333/002-3/DC |
| Reference Member State                          | United Kingdom |
| Member States concerned                        | Czech Republic, Germany, Hungary, Ireland, Italy, Poland, Slovenia and Spain |
| Marketing Authorisation Number(s)               | PL 31774/0002-3 |
| Name and address of the authorisation holder    | Bluefish Pharmaceuticals AB,  
Torsgatan 11, 111 23 Stockholm, Sweden |
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

S.  Active substance

ACTIVE SUBSTANCE – AMOXICILLIN TRIHYDRATE

INN:  Amoxicillin trihydrate

Chemical Name:  (2S,5R,6R)-6-[((R)-(−))2-Amino-2-(ρ-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate

Molecular Formula:  C_{16}H_{19}N_{3}O_{5}S·3H_{2}O

Molecular Weight:  419.4

Appearance:  A white or almost white, crystalline powder, slightly soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in fatty oils, chloroform and ether. It dissolves in dilute acids and dilute solutions of alkali hydroxides.

Amoxicillin trihydrate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance amoxicillin trihydrate are covered by a European Directorate for the Quality of Medicines (EDQM) certificate of suitability.

ACTIVE SUBSTANCE – POTASSIUM CLAVULANATE

INN:  Potassium clavulanate

Chemical Name:  (Z)-(2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate

Molecular Formula:  C_{8}H_{8}KNO_{5}

Molecular Weight:  237.3

Appearance:  A white or almost white, crystalline, hygroscopic powder, freely soluble in water, slightly soluble in alcohol and very slightly soluble in acetone.

Potassium clavulanate is the subject of a European Pharmacopoeia monograph.
All aspects of the manufacture and control of the active substance potassium clavulanate are covered by a European Directorate for the Quality of Medicines (EDQM) certificate of suitability.

P. Medicinal Product
Other Ingredients
Other ingredients consist of pharmaceutical excipients microcrystalline cellulose (AVICEL Ph 102), croscarmellose sodium, purified talc, magnesium stearate, hypromellose (E-15), ethylcellulose, propylene glycol, hydroxypropyl cellulose and titanium dioxide.

All excipients comply with their respective European Pharmacopoeia monograph. Suitable batch analysis data have been provided for each excipient, showing compliance with their respective monograph.

None of the excipients is sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development
The objective of the development programme was to formulate stable, efficacious and tolerable film-coated tablets containing amoxicillin trihydrate and potassium clavulanate that can be considered generic medicinal products of Augmentin 625mg and 1g Film-coated Tablets (GlaxoSmithKline, UK).

A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of both strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specifications proposed for both strengths are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Container-Closure System
Both strengths of tablets are packaged in transparent polyvinylchloride/aluminium blisters, which are then enclosed in a sealed aluminium pouch. Two pouches are packed per cardboard box. Pack sizes for both strengths are 7, 10, 12, 14, 20, 21 and 24 tablets. Not all pack sizes are to be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.
Stability of the product
Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 18 months, with the storage conditions ‘Do not store above 25°C’.

Suitable post approval stability commitments have been provided to follow-up the batches from the current studies.

Bioequivalence/bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a risk management plan for these products.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of marketing authorisations is recommended.

III.2 PRE-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of amoxicillin trihydrate and potassium clavulanate are well-known, no further studies are required and none have been provided.

The applicant’s non-clinical overview is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.
III.3 CLINICAL ASPECTS
Pharmacokinetics
In support of these applications, the marketing authorisation holder has submitted the following bioequivalence studies:

An open-label, randomised, two-period, two-treatment, two-sequence, single-dose, crossover study to compare the pharmacokinetics of the test product Co-amoxiclav 500/125mg Film-coated Tablets versus the reference product Augmentin 625mg Tablets (GlaxoSmithKline, UK) in healthy male volunteers under fasted conditions.

Volunteers were dosed with either treatment. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 10 hours post dose. The two treatment arms were separated by a 4-day washout period.

The results are presented below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Reference</th>
<th>Ratio T/R</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>7.594</td>
<td>7.409</td>
<td>1.004</td>
<td>0.8158-1.2357</td>
</tr>
<tr>
<td>AUC0-t</td>
<td>28.356</td>
<td>29.167</td>
<td>0.964</td>
<td>0.8341-1.1141</td>
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<tr>
<td>AUC0-inf</td>
<td>29.875</td>
<td>30.697</td>
<td>0.962</td>
<td>0.8412-1.1009</td>
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</table>

Clavulanic Acid (based on Geometric means)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Reference</th>
<th>Ratio T/R</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>665.915</td>
<td>650.863</td>
<td>1.036</td>
<td>0.9245-1.1603</td>
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<tr>
<td>AUC0-t</td>
<td>1530.408</td>
<td>1474.264</td>
<td>1.035</td>
<td>0.9527-1.1215</td>
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<tr>
<td>AUC0-inf</td>
<td>1667.490</td>
<td>1625.227</td>
<td>1.020</td>
<td>0.9504-1.0947</td>
</tr>
</tbody>
</table>

The test and reference products are within conventional 90% CI limits of 80-125% for amoxicillin and clavulanic acid. In conclusion, bioequivalence has been shown between the test and reference products.

An open-label, randomised, two-period, two-treatment, two-sequence, single-dose, crossover study to compare the pharmacokinetics of the test product Co-amoxiclav 875/125mg Film-coated Tablets versus the reference product Augmentin 1g Tablets (GlaxoSmithKline, UK) in healthy male volunteers under fasted conditions.

Volunteers were dosed with either treatment. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 12 hours post dose. The two treatment arms were separated by a 5-day washout period.

The results are presented below:

<table>
<thead>
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<th>Parameter</th>
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<th>Reference</th>
<th>Ratio T/R %</th>
<th>90% CI</th>
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</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>12.2647</td>
<td>12.9345</td>
<td>94.82</td>
<td>81.39-110.47</td>
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<tr>
<td>AUC0-t</td>
<td>43.6787</td>
<td>44.6915</td>
<td>97.73</td>
<td>84.77-112.68</td>
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<tr>
<td>AUC0-inf</td>
<td>45.9513</td>
<td>46.6804</td>
<td>98.44</td>
<td>85.81-112.92</td>
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</tbody>
</table>

Clavulanic Acid (based on Geometric means)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Reference</th>
<th>Ratio T/R %</th>
<th>90% CI</th>
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</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>2.5587</td>
<td>2.4037</td>
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<tr>
<td>AUC0-t</td>
<td>6.1082</td>
<td>5.8769</td>
<td>103.94</td>
<td>89.52-120.67</td>
</tr>
<tr>
<td>AUC0-inf</td>
<td>6.2991</td>
<td>6.0357</td>
<td>105.74</td>
<td>91.13-122.70</td>
</tr>
</tbody>
</table>
The test and reference products are within conventional 90% CI limits of 80-125% for amoxicillin and clavulanic acid. In conclusion, bioequivalence has been shown between the test and reference products.

**Efficacy**
No new data on the efficacy of either active substance are submitted and none are required for these types of applications.

**Safety**
No new or unexpected safety issues were raised by the bioequivalence data.

**SPC, PIL, Labels**
The SPC, PIL and labels are medically acceptable. The SPCs are consistent with those for the originator products.

**Conclusion**
The grant of marketing authorisations is recommended.

**IV OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT**

**QUALITY**
The important quality characteristics of Co-amoxiclav 500/125mg and 875/125mg Film-coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the risk-benefit balance.

**PRECLINICAL**
No new preclinical data were submitted and none are required for applications of this type.

**EFFICACY**
Bioequivalence has been demonstrated between the applicant’s Co-amoxiclav 500/125mg and 875/125mg Film-coated Tablets and their respective originator products.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those for the originator products, Augmentin 625mg and 1g Tablets (GlaxoSmithKline, UK).

**RISK-BENEFIT ASSESSMENT**
The quality of the products is acceptable, and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the originator products are interchangeable. Extensive clinical experience with amoxicillin and clavulanic acid is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
# Module 6

## STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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