Public Assessment Report

Co-Amoxiclav 500/100mg Powder solution for injection or infusion
Co-Amoxiclav 1000/200mg Powder solution for injection or infusion

Amoxicillin sodium and clavulanate potassium

PL 24610/0001
PL 24610/0002

Bowmed Ltd

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Lay Summary

The MHRA today granted Bowmed Ltd marketing authorisations (licenses) for the medicinal products Co-amoxiclav 500/100mg Powder for solution for injection or infusion (PL 24610/001) and Co-amoxiclav 100/200mg Powder for solution for injection or infusion (PL 24610/002) on. The products are prescription-only medicines.

The products contain two active ingredients, amoxicillin sodium and clavulanate potassium. Amoxicillin is an antibiotic agent with a notably broad spectrum of activity against the commonly occurring bacterial pathogens in general practice and hospital. The β-lactamase inhibitory action of clavulanate extends the spectrum of amoxicillin to embrace a wider range of organisms including many resistant to other β-lactam antibiotics. Co-amoxiclave is used to treat respiratory infections, infections of the GI tract and wound infections.

Scientific Discussion

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK, granted market authorisations for the medicinal products Co-amoxiclav 500/100mg Powder for solution for injection or infusion (PL 24610/001) and Co-amoxiclav 100/200mg Powder for solution for injection or infusion (PL 24610/002) on. The products are prescription-only medicines.

These are two strengths of Co-amoxiclav, submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC. Co-amoxiclav is claimed to be a generic medical products of Augmentin 600mg powder for solution for injection or infusion and Augmentin 1200mg powder for solution for injection or infusion, licences held by GlaxoSmithKline UK (PL 00038/0320-1) which has been marketed in the EU for > 10 years.

The products contain two active ingredients, amoxicillin sodium and clavulanate potassium. Amoxicillin is an antibiotic agent with a notably broad spectrum of activity against the commonly occurring bacterial pathogens in general practice and hospital. The β-lactamase inhibitory action of clavulanate extends the spectrum of amoxicillin to embrace a wider range of organisms including many resistant to other β-lactam antibiotics. Co-amoxiclave is used to treat respiratory infections, infections of the GI tract and wound infections.

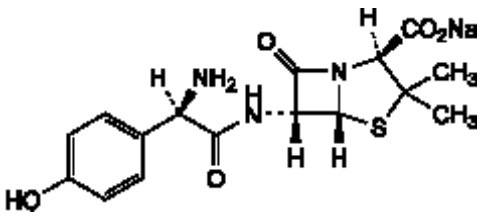
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

A: Amoxicillin sodium (sterile)

The AIM has been granted a Certificate of Suitability from the EDQM for this drug substance. A copy of this certificate has been provided as part of the annex to the MAA form.

Structure



$C_{16}H_{18}N_3NaO_5S$ M_r 387.4
CAS: 26787-78-0

Appearance: A white or almost white powder, very hygroscopic.

Solubility: Very soluble in water, sparingly soluble in ethanol, very slightly soluble in acetone.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Amoxicillin sodium is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

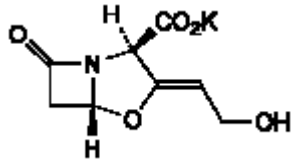
Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a retest period of one year when stored in 25L aluminium cans, plugged with 100mm chlorobuthylic rubber closures and sealed with aluminium caps.

B: Clavulanate potassium sterile

The AIM has submitted full data (open and restricted parts) pertaining to the production of sterile clavulanate potassium in module 3.2.S of the CTD. The QOS for the production of sterile clavulanate potassium is provided as part of the QOS of the entire dossier.



$C_8H_8KNO_5$ M_r 237.3
CAS: 61177-45-5

Appearance: white or almost white, crystalline powder, hygroscopic.
Solubility: freely soluble in water, slightly soluble in alcohol, very slightly soluble in acetone. The specific rotation is +53 - +63°C calculated with reference to the anhydrous substance. Clavulanic shows two asymmetric centres present on the nucleus.

A satisfactory description of the manufacture of clavulanate potassium has been provided.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Clavulante potassium is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a retest period of 24 months.

DRUG PRODUCT

Other ingredients
There are no other ingredients in this product.

Composition of Co-amoxiclav powder for solution for injection/infusion

Ingredient	Function	Ref	500/100 (mg)	1000/200 (mg)
Amoxicillin sodium sterile Equivalent to amoxicillin	Active ingredient	PhEur	530.1 500.00	1030.2 1000.00
Potassium Clavulanate sterile Equivalent to clavulanic acid	Active ingredient	PhEur	119.13 100.00	238.25 200.00

This combination of drug substances is the same as that for the cross reference licence and other products granted UK licences and so drug-drug compatibility studies do not need to be performed. Drug-excipient compatibility studies do not need to be performed as there are no excipients in the drug product.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

Dissolution and impurity profiles
Dissolution and impurity profiles for both strengths of drug product were found to be similar to those for the reference products.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data

have been provided and comply with the release specification, including data for sterility of product. Certificates of analysis have been provided for any working standards used.

Container Closure System
The product is presented as 10mL and 20mL clear glass vials in cartons of 10 vials. The vials are composed of Type III glass vials with a chlorobutyl rubber stopper and sealed with an aluminium ring. This is the same as the reference product (packaged in either type I or type III glass vials). The use of type III glass vials is acceptable for sterile powders for infusion/injection for parenteral use.

Stability
Satisfactory stability data was provided to support a shelf-life of 24 months with the following conditions

Store in a dry place
Do not store above 25°C

ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

The requirements for the products being generic medical products of the reference products have been met. A Marketing Authorisation was granted.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for an application of this type.

MEDICAL ASSESSMENT

CLINICAL PHARMACOLOGY

The product is an antibiotic/chemotherapeutic (penicillin with broad spectrum of action) (J01CR)

Mechanism of action:

Amoxicillin:
Amoxicillin is an acid stable aminopenicillin that is susceptible to hydrolysis by common β-lactamase enzymes.

Clavulanic acid:
Clavulanic acid is a β-lactam molecule that is able to inhibit many of the most commonly occurring β-lactamases such as staphylococcal penicillinases and enzymes of the TEM, OXA, SHV families (including many of the extended spectrum β-lactamases of these group). Thus, the combination of amoxicillin with clavulanic acid maintains the activity of the aminopenicillin against organisms that produce sufficient quantities of these enzymes that would otherwise render it inactive.
However, clavulanic acid is not able to inhibit the AmpC (Class I) β-lactamases that may be produced by certain Gram-negative bacilli or the metallo- β-lactamases (such as carbapenemases). Therefore, organisms that are normally susceptible to amoxicillin but have required the ability to produce any of these enzymes in amounts sufficient to render amoxicillin inactive would not be susceptible to Co-amoxiclav.

PHARMACOKINETICS

The pharmacokinetics of the two components of Co-amoxiclav are closely matched. Both clavulanate and amoxicillin have low levels of serum binding; about 70% remains free in the serum. Doubling the dosage of Co-amoxiclav approximately doubles the serum levels achieved. No bioequivalence study was performed and the product is a powder for solution for injection or infusion.

EFFICACY

Efficacy is reviewed in the Clinical Expert Report. The reference product is established and the application depends upon the ability to show bioequivalence with the reference product.

SAFETY

Safety is reviewed in the Clinical Expert Report. The reference product is established and the application depends upon the ability to show bioequivalence with the reference product.

EXPERT REPORT

The expert report is written by a medically qualified pharmaceutical consultant and is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS
This is satisfactory.

PATIENT INFORMATION LEAFLET
This is satisfactory.

CONCLUSIONS
A marketing authorisation was granted.

Overall Conclusion and Risk/Benefit Analysis

Quality

The important quality characteristics of Co-amoxiclav 500/100mg Powder for solution for injection or infusion and Co-amoxiclav 100/200mg Powder for solution for injection or infusion 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 benefit/risk balance.

Pre-Clinical

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

Clinical

The products were found to meet the requirements of generic medical products of the reference product.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Augmentin.

Risk/Benefit Analysis

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The risk benefit is, therefore, considered to be positive.

Steps Taken During Assessment

1	The MHRA received the application on 1st June 2005.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 14th July 2005.
3	Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 15th march 2006, 10th May 2007 and 29th August 2007 and on the medical assessment on 16th March 2006.
4	The applicant provided further information in regard to the quality assessment on 21 October 2006, 1 August 2007and 24th October 2007 and on the medical assessment on 27th August 2006.
5	The application was determined on 2nd November 2007.

Steps Taken after Assessment

None

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-amoxiclav 500mg/100mg Powder for solution for Injection or Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:
Amoxicillin 500 mg (as amoxicillin sodium).
Clavulanic acid 100 mg (as clavulanate potassium).

3 PHARMACEUTICAL FORM

Powder for solution for injection or infusion
Glass vial containing white powder

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Co-amoxiclav is an antibiotic agent with a notably broad spectrum of activity against the commonly occurring bacterial pathogens in general practice and hospital. The β-lactamase inhibitory action of clavulanate extends the spectrum of amoxicillin to embrace a wider range of organisms including many resistant to other β-lactam antibiotics.
Co-amoxiclav for Injection is indicated for short-term treatment of bacterial infections at the following sites when amoxicillin-resistant β-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*.

Prophylaxis of wound infection associated with surgical procedures in particular gastrointestinal, pelvic, major head and neck surgery and after limb amputation for infection.
- A comprehensive list of sensitive organisms is provided in Section 5.
* Some members of these species of bacteria produce β-lactamase, rendering them insensitive to amoxicillin alone.
Mixed infections caused by amoxicillin-susceptible organisms in conjunction with Co-amoxiclav-susceptible β-lactamase-producing organisms may be treated with Co-amoxiclav. These infections should not require the addition of another antibiotic resistant to β-lactamases.

4.2 Posology and method of administration

For intravenous use.
Dosages for the treatment of infection
Adults and children over 12 years:
Usually 1.2g eight hourly. In more serious infections, increase frequency to six-hourly intervals.
Children 3 months-12 years:
Usually 30 mg/kg * Co-amoxiclav eight hourly. In more serious infections, increase frequency to six-hourly intervals.
Children 0-3 months:
30 mg/kg* Co-amoxiclav every 12 hours in premature infants and in full-term infants during the perinatal period, increasing to eight hours thereafter.
*Each 30 mg Co-amoxiclav provides Co-amoxiclav 25/5.
Adult dosage for surgical prophylaxis
The usual dose is Co-amoxiclav 1.2g given at the induction of anaesthesia. Operations where there is a high risk of infection, e.g. colorectal surgery, may require three, and up to four, doses of Co-amoxiclav 1.2g in a 24-hour period. These doses are usually given at 0, 8, 16 (and 24) hours. This regimen can be continued for several days if the procedure has a significantly increased risk of infection. Clear clinical signs of infection at operation will require a normal course of intravenous or oral Co-amoxiclav therapy post-operatively.
Dosage in renal impairment
Adults:

Mild impairment (creatinine clearance >30 ml/min)	Moderate impairment (creatinine clearance 10-30 ml/min)	Severe impairment (creatinine clearance <10 ml/min)
No change in dosage.	1.2g IV stat., followed by 600mg IV 12 hourly.	1.2g IV stat., followed by 600mg IV 24 hourly. Dialysis decreases serum concentrations of Co-amoxiclav and an additional 600mg IV dose may need to be given during dialysis and at the end of

		dialysis.

Children
Similar reductions in dosage should be made for children.
Dosage in 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
Co-amoxiclav may be administered either by intravenous injection or by intermittent infusion. It is not suitable for intramuscular administration.
Co-amoxiclav should be given by slow intravenous injection over a period of three to four minutes. It may be injected directly into a vein or via a drip tube.
Alternatively, Co-amoxiclav may be infused in Water for Injections BP or Sodium Chloride Intravenous Injection BP (0.9% w/v). For instructions on reconstitution and dilution of the product before administration, see section 6.6.
Duration of therapy should be appropriate to the indication and should not exceed 14 days without review.

4.3 Contraindications
Penicillin hypersensitivity. Attention should be paid to possible cross-sensitivity with other β-lactam antibiotics, e.g. cephalosporins.
A previous history of Co-amoxiclav- or penicillin-associated jaundice/hepatic dysfunction.

4.4 Special warnings and precautions for use
Changes 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 Section 4.2).
If the parenteral administration of high doses is necessary, the sodium content must be taken into account in patients on a sodium restricted diet.
In patients with reduced urine output crystalluria has been observed very rarely, predominantly with parenteral therapy. During 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 Section 4.9 Overdose). Amoxicillin has been reported to precipitate in bladder catheters after intravenous administration of large doses. A regular check of patency should be maintained.
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 Section 4.3).

Erythematous rashes have been associated with glandular fever in patients receiving amoxicillin.
Prolonged use may also occasionally result in overgrowth of non-susceptible organisms.

4.5 Interaction with other medicinal products and other forms of interaction

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.
In common with other broad-spectrum antibiotics, Co-amoxiclav may reduce the efficacy of oral contraceptives and patients should be warned accordingly.
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 Co-amoxiclav and allopurinol.

4.6 Pregnancy and lactation

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 Co-amoxiclav may be associated with an increased risk of necrotising enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the physician.
Co-amoxiclav may be administered during the period of lactation. With the exception of the risk of sensitisation, associated with the excretion of trace quantities in breast milk, there are no known detrimental effects for the breast-fed infant.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Side effects are uncommon and mainly of a mild and transitory nature.
Gastrointestinal reactions:
Diarrhoea, indigestion, nausea, vomiting, and mucocutaneous candidiasis have been reported. Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) has been reported rarely. Nausea, although uncommon, is more often associated with higher oral dosages. If gastrointestinal side effects occur with oral therapy they may be reduced by taking Co-amoxiclav at the start of meals.
Superficial tooth discolouration has been reported rarely, mostly with Co-amoxiclav suspension. It can usually be removed by brushing.
Renal and urinary tract disorders:
Crystalluria has been reported very rarely (See Section 4.9 Overdose).
Genito-urinary effects:
Vaginal itching, soreness and discharge may occur.
Hepatic effects:

Moderate and asymptomatic rises in AST and/or ALT and alkaline phosphatases have been reported occasionally. Hepatitis and cholestatic jaundice have been reported rarely. These hepatic reactions have been reported more commonly with Co-amoxiclav than with other penicillins. Hepatic reactions have been reported more frequently in males and elderly patients, particularly those over 65 years. The risk increases with duration of treatment longer than 14 days. These reactions have been very rarely reported in children. Signs and symptoms usually occur during or shortly after treatment but in some cases may not occur until several weeks after treatment has ended. Hepatic reactions are usually reversible but they may be severe and, very rarely, deaths have been reported.

Hypersensitivity reactions:

Urticarial and erythematous skin rashes sometimes occur. Rarely erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative dermatitis, acute generalised exanthematous pustulosis (AGEP), serum sickness-like syndrome and hypersensitivity vasculitis have been reported. Treatment should be discontinued if one of these disorders occurs. In common with other β-lactam antibiotics angioedema and anaphylaxis have been reported. Interstitial nephritis can occur rarely.

Haematological effects:

As with other β-lactams transient leucopenia (including neutropenia and agranulocytosis), thrombocytopenia and haemolytic anaemia have been reported rarely. Prolongation of bleeding time and prothrombin time has also been reported rarely (see Section 4.5).

CNS disorders:

CNS effects have been seen very rarely. These include reversible hyperactivity, dizziness, headache and convulsions. Convulsions may occur with impaired renal function or in those receiving high doses.

Local:

Thrombophlebitis at the site of injection has been reported occasionally.

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 water electrolyte balance. Co-amoxiclav 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

Antibiotic/chemotherapeutic (penicillin with broad spectrum of action) (J01CR)

Mechanism of action:

Amoxicillin:

Amoxicillin is an acid stable aminopenicillin that is susceptible to hydrolysis by common β-lactamase enzymes.

Clavulanic acid:

Clavulanic acid is a β-lactam molecule that is able to inhibit many of the most commonly occurring β-lactamases such as staphylococcal penicillinases and enzymes of the TEM, OXA, SHV families (including many of the extended spectrum β-lactamases of these group). Thus, the combination of amoxicillin with clavulanic acid maintains the activity of the aminopenicillin against organisms that produce sufficient quantities of these enzymes that would otherwise render it inactive.
However, clavulanic acid is not able to inhibit the AmpC (Class I) β-lactamases that may be produced by certain Gram-negative bacilli or the metallo- β-lactamases (such as carbapenemases). Therefore, organisms that are normally susceptible to amoxicillin but have required the ability to produce any of these enzymes in amounts sufficient to render amoxicillin inactive would not be susceptible to Co-amoxiclav.

Antibacterial spectrum

MIC breakpoints

The MIC breakpoints according to the NCCLS criteria and methodology that separates susceptible (S) organisms from those that are intermediately susceptible (I) or resistant (R) are:
Enterobacteriaceae: S ≤ 8/4 mg/L
I = 16/8 mg/L
R ≥ 32/16 mg/L
Staphylococci: S ≤ 4/2 mg/L
R ≥ 8/4 mg/L
Haemophilus influenzae: S ≤ 4/2 mg/L
R ≥ 8/4 mg/L
Streptococcus pneumoniae: S ≤ 0.5/0.25 mg/L
I = 1/0.5 mg/L
R ≥ 2/1 mg/L

BSAC criteria are as follows (expressed as amoxicillin):
Enterobacteriaceae: S ≤ 8 mg/L
R ≥ 16 mg/L
In UTI: S ≤ 32 mg/L
R ≥ 64 mg/L
Haemophilus influenzae, Moraxella catarrhalis: S ≤ 1 mg/L
R ≥ 2 mg/L
Spectrum of action of Co-amoxiclav:
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. This information gives only approximate guidance on the probabilities whether micro-organsims will be susceptible to Co-amoxiclav or not. As far as possible the information on the European range of acquired resistance for the individual micro-organism is indicated in brackets.

Micro-organisms	**Resistance-prevalence in EU***
SUSCEPTIBLE	
Gram positive aerobes	
E. faecalis	
S. aureus methicillin-susceptible	
S. pneumoniae	0 - 26%*
S. pyrogenes	
Gram negaive organsims	
E. coli	5 – 20%*
K. pneumoniae	7%*
H. influenzae	2%
M. catarrhalis	
P. mirablis *N. gonorrhoeae*	Up to 34%*
Anaerobes	
B. fragilis	
C. perfringens	
Peptostreptococcus spp.	
RESISTANT	
Gram positive organisms	
E. faecium	
S. aureus methicillin resistant	
Gram-negative organsims	
E. aerogenes	
E. cloacae	
M. morganii	
P. aeruginosa	
Serratia spp.	
P. rettgeri	

Others	
Legionellae	
Chlamydia spp.	
Mycoplasma spp.	
Ricketsia spp.	

* It is recommended thatlocal information on the epidemiology of resistant micro-organisms should be consulted.

Resistance

Organisms that are normally resistant to amoxycillin by non-beta-lactamase-mediated mechanisms (such as impermeability, altered penicillin-binding proteins or drug efflux pumps) or via the manufacture of enzymes that are not inhibited by clavulanic acid would also be resistant to amoxycillin/clavulanate.

5.2 Pharmacokinetic properties

The pharmacokinetics of the two components of Co-amoxiclav are closely matched. Both clavulanate and amoxicillin have low levels of serum binding; about 70% remains free in the serum. Doubling the dosage of Co-amoxiclav approximately doubles the serum levels achieved.

5.3 Preclinical safety data

Acute toxicity:

Investigations of the acute toxicity (LD_{50}) of amoxicillin and clavulanic acid in adult animals and neonates have confirmed very low toxicity potential. The LD_{50} of clavulanic acid (potassium salt) is determined by the potassium content. Administration of clavulanic acid (potassium salt) together does not result in any unexpected or synergistic toxicity.

Chronic toxicity/subchronic toxicity

Not relevant

Mutagenic and tumorigenic potential

In vitro and in vivo studies did not reveal any signs of any mutagenic effects of the combination of amoxicillin and clavulanic acid.

Reproductive toxicity

After treatment of various infections in pregnant women (approximately 560 pregnancies) with Co-amoxiclav, no increased occurrence of malformations was observed. Amoxicillin and clavulanic acid diffuse through the placenta and are excreted into breast milk.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. Co-amoxiclav should not be mixed

with blood products, other proteinaceous fluids such as protein hydrolysates or with intravenous lipid emulsions.
If Co-amoxiclav is prescribed concurrently with an aminoglycoside, the antibiotics should not be mixed in the syringe, intravenous fluid container or giving set because loss of activity of the aminoglycoside can occur under these conditions.

6.3 Shelf life

Shelf-life: 2 years
Shelf-life after dilution or reconstitution:
Chemical and physical in-use stability has been demonstrated as shown in the following table:

Infusion Fluid	Stability (hours)	
	5° C	25° C
Water for injections	8	4
Sodium chloride intravenous infusion 0.9%	8	4
Sodium lactate intravenous infusion (M/6)	-	4
Ringers Solution	-	3
Hartmann's Solution; Ringer-Lactate Solution	-	3
Potassium chloride and Sodium chloride intravenous infusion	-	3

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product shoud be used immediately. If not used, immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Clear glass vial (Ph.Eur. Type III) fitted with a chlorobutyl rubber stopper and an aluminium ring.
1, 5, 10, 20 or 50 vials are contained in a cardboard box. Not all pack sizes may be marketed

6.6 Special precautions for disposal

Reconstitution:
Dissolve in 20ml Water for Injections BP. A clear, colourless solution is produced.
Dilution for infusion:
Add without delay the reconstituted solution to 100 ml infusion fluid (e.g. using a minibag or in-line burette). Infuse over 30-40 minutes and complete within four hours of reconstitution. For other appropriate infusion fluids, see Package Enclosure Leaflet.

Co-amoxiclav is less stable in infusions containing glucose, dextran or bicarbonate. Reconstituted solution should therefore not be added to such infusions but may be injected into the drip tubing over a period of three to four minutes.

7 MARKETING AUTHORISATION HOLDER

Bowmed Limited
113 Promenade
Cheltenham
GL50 1NW

8 MARKETING AUTHORISATION NUMBER(S)

PL 24610/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02/11/2007

10 DATE OF REVISION OF THE TEXT

02/11/2007

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-amoxiclav 1000mg/200mg Powder for solution for Injection or Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:
Amoxicillin 1000 mg (as amoxicillin sodium).
Clavulanic acid 200 mg (as clavulanate potassium).

3 PHARMACEUTICAL FORM

Powder for solution for injection or infusion
Glass vial containing white powder

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Co-amoxiclav is an antibiotic agent with a notably broad spectrum of activity against the commonly occurring bacterial pathogens in general practice and hospital. The β-lactamase inhibitory action of clavulanate extends the spectrum of amoxicillin to embrace a wider range of organisms including many resistant to other β-lactam antibiotics.
Co-amoxiclav for Injection is indicated for short-term treatment of bacterial infections at the following sites when amoxicillin-resistant β-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*.

Prophylaxis of wound infection associated with surgical procedures in particular gastrointestinal, pelvic, major head and neck surgery and after limb amputation for infection.
- A comprehensive list of sensitive organisms is provided in Section 5.
* Some members of these species of bacteria produce β-lactamase, rendering them insensitive to amoxicillin alone.
Mixed infections caused by amoxicillin-susceptible organisms in conjunction with Co-amoxiclav-susceptible β-lactamase-producing organisms may be treated with Co-amoxiclav. These infections should not require the addition of another antibiotic resistant to β-lactamases.

4.2 Posology and method of administration

For intravenous use.
Dosages for the treatment of infection
Adults and children over 12 years:
Usually 1.2g eight hourly. In more serious infections, increase frequency to six-hourly intervals.
Children 3 months-12 years:
Usually 30 mg/kg * Co-amoxiclav eight hourly. In more serious infections, increase frequency to six-hourly intervals.
Children 0-3 months:
30 mg/kg* Co-amoxiclav every 12 hours in premature infants and in full-term infants during the perinatal period, increasing to eight hours thereafter.
*Each 30 mg Co-amoxiclav provides Co-amoxiclav 25/5.
Adult dosage for surgical prophylaxis
The usual dose is Co-amoxiclav 1.2g given at the induction of anaesthesia. Operations where there is a high risk of infection, e.g. colorectal surgery, may require three, and up to four, doses of Co-amoxiclav 1.2g in a 24-hour period. These doses are usually given at 0, 8, 16 (and 24) hours. This regimen can be continued for several days if the procedure has a significantly increased risk of infection. Clear clinical signs of infection at operation will require a normal course of intravenous or oral Co-amoxiclav therapy post-operatively.
Dosage in renal impairment
Adults:

Mild impairment (creatinine clearance >30 ml/min)	Moderate impairment (creatinine clearance 10-30 ml/min)	Severe impairment (creatinine clearance <10 ml/min)
No change in dosage.	1.2g IV stat., followed by 600mg IV 12 hourly.	1.2g IV stat., followed by 600mg IV 24 hourly. Dialysis decreases serum concentrations of Co-amoxiclav and an additional 600mg IV dose may need to be given during dialysis and at the end of

		dialysis.

Children
Similar reductions in dosage should be made for children.
Dosage in 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
Co-amoxiclav may be administered either by intravenous injection or by intermittent infusion. It is not suitable for intramuscular administration.
Co-amoxiclav should be given by slow intravenous injection over a period of three to four minutes. It may be injected directly into a vein or via a drip tube.
Alternatively, Co-amoxiclav may be infused in Water for Injections BP or Sodium Chloride Intravenous Injection BP (0.9% w/v). For instructions on reconstitution and dilution of the product before administration, see section 6.6.
Duration of therapy should be appropriate to the indication and should not exceed 14 days without review.

4.3 Contraindications
Penicillin hypersensitivity. Attention should be paid to possible cross-sensitivity with other β-lactam antibiotics, e.g. cephalosporins.
A previous history of Co-amoxiclav- or penicillin-associated jaundice/hepatic dysfunction.

4.4 Special warnings and precautions for use
Changes 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 Section 4.2).
If the parenteral administration of high doses is necessary, the sodium content must be taken into account in patients on a sodium restricted diet.
In patients with reduced urine output crystalluria has been observed very rarely, predominantly with parenteral therapy. During 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 Section 4.9 Overdose). Amoxicillin has been reported to precipitate in bladder catheters after intravenous administration of large doses. A regular check of patency should be maintained.
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 Section 4.3).

Erythematous rashes have been associated with glandular fever in patients receiving amoxicillin.
Prolonged use may also occasionally result in overgrowth of non-susceptible organisms.

4.5 Interaction with other medicinal products and other forms of interaction

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.
In common with other broad-spectrum antibiotics, Co-amoxiclav may reduce the efficacy of oral contraceptives and patients should be warned accordingly.
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 Co-amoxiclav and allopurinol.

4.6 Pregnancy and lactation

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 Co-amoxiclav may be associated with an increased risk of necrotising enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the physician.
Co-amoxiclav may be administered during the period of lactation. With the exception of the risk of sensitisation, associated with the excretion of trace quantities in breast milk, there are no known detrimental effects for the breast-fed infant.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Side effects are uncommon and mainly of a mild and transitory nature.
Gastrointestinal reactions:
Diarrhoea, indigestion, nausea, vomiting, and mucocutaneous candidiasis have been reported. Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) has been reported rarely. Nausea, although uncommon, is more often associated with higher oral dosages. If gastrointestinal side effects occur with oral therapy they may be reduced by taking Co-amoxiclav at the start of meals.
Superficial tooth discolouration has been reported rarely, mostly with Co-amoxiclav suspension. It can usually be removed by brushing.
Renal and urinary tract disorders:
Crystalluria has been reported very rarely (See Section 4.9 Overdose).
Genito-urinary effects:
Vaginal itching, soreness and discharge may occur.
Hepatic effects:

Moderate and asymptomatic rises in AST and/or ALT and alkaline phosphatases have been reported occasionally. Hepatitis and cholestatic jaundice have been reported rarely. These hepatic reactions have been reported more commonly with Co-amoxiclav than with other penicillins. Hepatic reactions have been reported more frequently in males and elderly patients, particularly those over 65 years. The risk increases with duration of treatment longer than 14 days. These reactions have been very rarely reported in children. Signs and symptoms usually occur during or shortly after treatment but in some cases may not occur until several weeks after treatment has ended. Hepatic reactions are usually reversible but they may be severe and, very rarely, deaths have been reported.

Hypersensitivity reactions:

Urticarial and erythematous skin rashes sometimes occur. Rarely erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative dermatitis, acute generalised exanthematous pustulosis (AGEP), serum sickness-like syndrome and hypersensitivity vasculitis have been reported. Treatment should be discontinued if one of these disorders occurs. In common with other β-lactam antibiotics angioedema and anaphylaxis have been reported. Interstitial nephritis can occur rarely.

Haematological effects:

As with other β-lactams transient leucopenia (including neutropenia and agranulocytosis), thrombocytopenia and haemolytic anaemia have been reported rarely. Prolongation of bleeding time and prothrombin time has also been reported rarely (see Section 4.5).

CNS disorders:

CNS effects have been seen very rarely. These include reversible hyperactivity, dizziness, headache and convulsions. Convulsions may occur with impaired renal function or in those receiving high doses.

Local:

Thrombophlebitis at the site of injection has been reported occasionally.

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 water electrolyte balance. Co-amoxiclav 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

Antibiotic/chemotherapeutic (penicillin with broad spectrum of action) (J01CR)

Mechanism of action:

Amoxicillin:

Amoxicillin is an acid stable aminopenicillin that is susceptible to hydrolysis by common β-lactamase enzymes.

Clavulanic acid:

Clavulanic acid is a β-lactam molecule that is able to inhibit many of the most commonly occurring β-lactamases such as staphylococcal penicillinases and enzymes of the TEM, OXA, SHV families (including many of the extended spectrum β-lactamases of these group). Thus, the combination of amoxicillin with clavulanic acid maintains the activity of the aminopenicillin against organisms that produce sufficient quantities of these enzymes that would otherwise render it inactive.
However, clavulanic acid is not able to inhibit the AmpC (Class I) β-lactamases that may be produced by certain Gram-negative bacilli or the metallo- β-lactamases (such as carbapenemases). Therefore, organisms that are normally susceptible to amoxicillin but have required the ability to produce any of these enzymes in amounts sufficient to render amoxicillin inactive would not be susceptible to Co-amoxiclav.

Antibacterial spectrum

MIC breakpoints

The MIC breakpoints according to the NCCLS criteria and methodology that separates susceptible (S) organisms from those that are intermediately susceptible (I) or resistant (R) are:
Enterobacteriaceae: S ≤ 8/4 mg/L
I = 16/8 mg/L
R ≥ 32/16 mg/L
Staphylococci: S ≤ 4/2 mg/L
R ≥ 8/4 mg/L
Haemophilus influenzae: S ≤ 4/2 mg/L
R ≥ 8/4 mg/L
Streptococcus pneumoniae: S ≤ 0.5/0.25 mg/L
I = 1/0.5 mg/L
R ≥ 2/1 mg/LBSAC criteria are as follows (expressed as amoxicillin):
Enterobacteriaceae: S ≤ 8 mg/L
R ≥ 16 mg/L
In UTI: S ≤ 32 mg/L
R ≥ 64 mg/L
Haemophilus influenzae, Moraxella catarrhalis: S ≤ 1 mg/L
R ≥ 2 mg/L

Spectrum of action of Co-amoxiclav:

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. This information gives only approximate guidance on the probabilities whether micro-organsims will be susceptible to Co-amoxiclav or not. As far as possible the information on the European range of acquired resistance for the individual micro-organism is indicated in brackets.

Micro-organisms	**Resistance-prevalence in EU***
SUSCEPTIBLE	
Gram positive aerobes	
E. faecalis	
S. aureus methicillin-susceptible	
S. pneumoniae	0 - 26%*

S. pyrogenes	
Gram negaive organsims	
E. coli	5 – 20%*
K. pneumoniae	7%*
H. influenzae	2%
M. catarrhalis	
P. mirablis *N. gonorrhoeae*	Up to 34%*
Anaerobes	
B. fragilis	
C. perfringens	
Peptostreptococcus spp.	
RESISTANT	
Gram positive organisms	
E. faecium	
S. aureus methicillin resistant	
Gram-negative organsims	
E. aerogenes	
E. cloacae	
M. morganii	
P. aeruginosa	
Serratia spp.	
P. rettgeri	

Others	
Legionellae	
Chlamydia spp.	
Mycoplasma spp.	
Ricketsia spp.	

* It is recommended thatlocal information on the epidemiology of resistant micro-organisms should be consulted.

Resistance

Organisms that are normally resistant to amoxycillin by non-beta-lactamase-mediated mechanisms (such as impermeability, altered penicillin-binding proteins or drug efflux pumps) or via the manufacture of enzymes that are not inhibited by clavulanic acid would also be resistant to amoxycillin/clavulanate.

5.2 Pharmacokinetic properties

The pharmacokinetics of the two components of Co-amoxiclav are closely matched. Both clavulanate and amoxicillin have low levels of serum binding; about 70% remains free in the serum. Doubling the dosage of Co-amoxiclav approximately doubles the serum levels achieved.

5.3 Preclinical safety data

Acute toxicity:

Investigations of the acute toxicity (LD_{50}) of amoxicillin and clavulanic acid in adult animals and neonates have confirmed very low toxicity potential. The LD_{50} of clavulanic acid (potassium salt) is determined by the potassium content. Administration of clavulanic acid (potassium salt) together does not result in any unexpected or synergistic toxicity.

Chronic toxicity/subchronic toxicity

Not relevant

Mutagenic and tumorigenic potential

In vitro and in vivo studies did not reveal any signs of any mutagenic effects of the combination of amoxicillin and clavulanic acid.

Reproductive toxicity

After treatment of various infections in pregnant women (approximately 560 pregnancies) with Co-amoxiclav, no increased occurrence of malformations was observed. Amoxicillin and clavulanic acid diffuse through the placenta and are excreted into breast milk.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. Co-amoxiclav should not be mixed

with blood products, other proteinaceous fluids such as protein hydrolysates or with intravenous lipid emulsions.
If Co-amoxiclav is prescribed concurrently with an aminoglycoside, the antibiotics should not be mixed in the syringe, intravenous fluid container or giving set because loss of activity of the aminoglycoside can occur under these conditions.

6.3 Shelf life

Shelf-life: 2 years
Shelf-life after dilution or reconstitution:
Chemical and physical in-use stability has been demonstrated as shown in the following table:

Infusion Fluid	Stability (hours)	
	5° C	25° C
Water for injections	8	4
Sodium chloride intravenous infusion 0.9%	8	4
Sodium lactate intravenous infusion (M/6)	-	4
Ringers Solution	-	3
Hartmann's Solution; Ringer-Lactate Solution	-	3
Potassium chloride and Sodium chloride intravenous infusion	-	3

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product shoud be used immediately. If not used, immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Clear glass vial (Ph.Eur. Type III) fitted with a chlorobutyl rubber stopper and an aluminium ring.
1, 5, 10, 20 or 50 vials are contained in a cardboard box. Not all pack sizes may be marketed

6.6 Special precautions for disposal

Reconstitution:
Dissolve in 20ml Water for Injections BP. A clear, colourless solution is produced.
Dilution for infusion:
Add without delay the reconstituted solution to 100 ml infusion fluid (e.g. using a minibag or in-line burette). Infuse over 30-40 minutes and complete within four hours of reconstitution. For other appropriate infusion fluids, see Package Enclosure Leaflet.

Co-amoxiclav is less stable in infusions containing glucose, dextran or bicarbonate. Reconstituted solution should therefore not be added to such infusions but may be injected into the drip tubing over a period of three to four minutes.

7 MARKETING AUTHORISATION HOLDER

Bowmed Limited
113 Promenade
Cheltenham
GL50 1NW

8 MARKETING AUTHORISATION NUMBER(S)

PL 24610/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02/11/2007

10 DATE OF REVISION OF THE TEXT

02/11/2007

Labels and Leaflet

PATIENT INFORMATION LEAFLET

Co-amoxiclav 500mg/100mg & 1000mg/200mg Powder for solution for injection or infusion

Read all of this leaflet carefully before you start using this medicine

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

In this leaflet:

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

Co-amoxiclav contains two active ingredients. One of these is called amoxicillin and the other is clavulanic acid. The vials contain no other ingredients.

Your medicine is available in two strengths: Co-amoxiclav 500mg/100mg and Co-amoxiclav 1000mg/200mg. Your doctor will decide which strength you need.

Co-amoxiclav is supplied in packs containing 1, 5, 10, 20 or 50 vials. Not all pack sizes may be marketed.

Co-amoxiclav is an antibiotic for treating infections. It belongs to a group of antibiotics called "penicillins". It works by killing the bacteria that can cause infections.

Co-amoxiclav can treat a wide range of bacterial infections including infections of the chest (bronchitis or pneumonia), tonsils (tonsilitis), sinuses (sinusitis), ears, skin (including animal bites), the bladder or urethra (the tube which carries urine from the bladder), kidneys, abdomen, teeth and gums (abcesses). It is also used to prevent infections which can occur after major surgery.

Marketing Authorisation Holder:
Bowmed Limited
113 Promenade
Cheltenham
UK

Manufacturer:
Istituto Biochimico Italiano Giovanni Lorenzini S.p.A.
Via di Fossignano
2 - Aprilia (LT)
Italy

[Laetus code]

2. BEFORE YOU ARE GIVEN CO-AMOXICLAV

You should not be given Co-amoxiclav if:

- you know that you are allergic to penicillin or any other antibiotics
- you have ever had a serious problem such as liver problems, when taking an antibiotic
- you have ever had a skin rash or swelling of the face or neck when taking any antibiotic

Tell your doctor or nurse if any of the above apply to you.

Please talk to your doctor if:

- you have been told that you have raised sodium levels in the blood
- you are taking any medicine containing potassium, potassium salts (used to flavour food instead of salt) or you are taking "water tablets" (diuretics) such as amiloride, triamterene or spironolactone
- you are being treated for kidney or liver problems
- you have glandular fever
- you are taking any medicine to prevent blood clots (such as warfarin)
- you are taking allopurinol for conditions such as gout.
- you are taking a contraceptive pill (as you will need to take extra contraceptive precautions such as using a condom).

If any of the above apply to you, your doctor may decide that you need another medicine instead of Co-amoxiclav, or that you need a different dose of Co-amoxiclav.

Pregnancy and breast-feeding
If you are pregnant or think you might be pregnant, or are breast-feeding, you must tell your doctor before taking this medicine.

Taking other medicines
Please tell your doctor if you are taking, or have recently taken, any other medicines including any that you may have bought without a prescription from a chemist or supermarket.

3. HOW CO-AMOXICLAV IS GIVEN

Your medicine will be given to you by injection or infusion into a vein (intravenously). Your doctor will decide how much you need and how often the injections should be given.

The usual dose for treating infection is:
Adults and children over 12 years: 1.2g given every 8 hours.
Children under 12 years: 30mg for each kilogram of body weight, every 8 hours.
Very young babies will be treated every 12 hours.

These doses can be increased in more serious infections. To prevent infections after an operation the usual adult dose is 1.2g before the operation, when you are given your anaesthetic.

If you think you have missed an injection, speak to your doctor or nurse.

You should not be given this product for longer than two weeks without your treatment being reviewed by your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Co-amoxiclav can have side effects.
See your doctor straight away if you:
- **get a swollen face or throat which causes difficulty in breathing**
- **notice your skin or the whites of your eyes turning yellow**
- **get severe diarrhoea with bleeding.**

All of these very serious side effects are very rare. Some of them can be delayed for several weeks after finishing the treatment.

Tell your doctor or nurse at once if you start to itch or get a rash.

Tell your doctor if you get any of the following side effects:
- nausea (feeling sick) or vomiting (being sick)
- stomach ache
- diarrhoea
- dizziness
- headache
- white patches in the mouth or vagina
- hyperactivity
- convulsions ("fits").

Rarely, some people may get a slight yellow/brown staining of the teeth. The staining usually disappears soon after treatment if teeth are brushed regularly.

Very rarely, this medicine may form crystals in the urine (usually only visible under a microscope). They may cause difficulty or discomfort in passing urine. You should therefore drink plenty of fluids such as water or non-alcoholic and non-caffeine containing drinks.

If you are having blood tests, tell your doctor you are having Co-amoxiclav. This is because Co-amoxiclav sometimes causes short-term changes in the number of blood cells.

If you suffer from any of these side effects or others not specified in this information leaflet, please tell your doctor or nurse.

5. STORING CO-AMOXICLAV

Do not store above 25°C.

Keep out of the reach and sight of children.

There is an expiry date on the label. The doctor or nurse will check that this date has not passed.

Leaflet prepared September 2007

INFORMATION FOR THE HEALTHCARE PROFESSIONAL

The following information is intended for medical or healthcare professionals only.

Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned below. Co-amoxiclav should not be mixed with blood products, other proteinaceous fluids such as protein hydrolysates or with intravenous lipid emulsions.

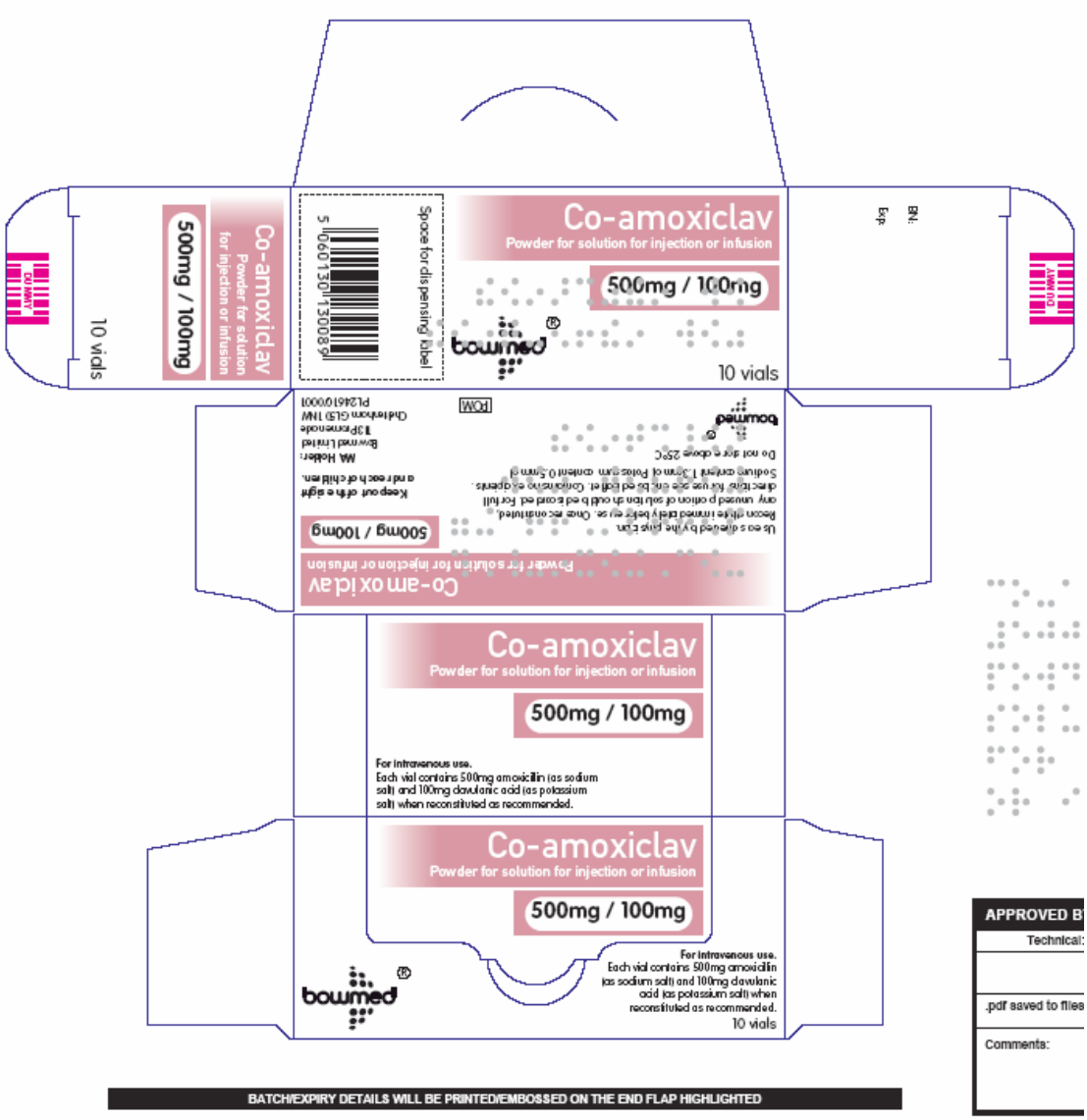
If Co-amoxiclav is prescribed concurrently with an aminoglycoside, the antibiotics should not be mixed in the syringe, intravenous fluid container or giving set because loss of activity of the aminoglycoside can occur under these conditions.

Storing Co-amoxiclav:
Do not store above 25°C.

Shelf-life
Shelf-life: 2 years
Shelf-life after dilution or reconstitution: Chemical and physical in-use stability has been demonstrated as shown in the table below.

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product shoud be used immediately. If not used, immediately, in-use storage times and conditions are the responsibility of the user.

Infusion Fluid	Stability (hours)	
	5° C	25° C
Water for injections	8	4
Sodium chloride intravenous infusion 0.9%	8	4
Sodium lactate intravenous infusion (M/6)	-	4
Ringers Solution	-	3
Hartmann's Solution; Ringer-Lactate Solution	-	3
Potassium chloride and Sodium chloride intravenous infusion	-	3


Co-amoxiclav
Powder for solution for injection or infusion
500mg / 100mg
10 vials
Space for dispensing label
BN:
Exp:
For intravenous use.
Each vial contains 500mg amoxicillin (as sodium salt) and 100mg clavulanic acid (as potassium salt) when reconstituted as recommended.
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bowmed
BATCH/EXPIRY DETAILS WILL BE PRINTED/EMBOSSED ON THE END FLAP HIGHLIGHTED
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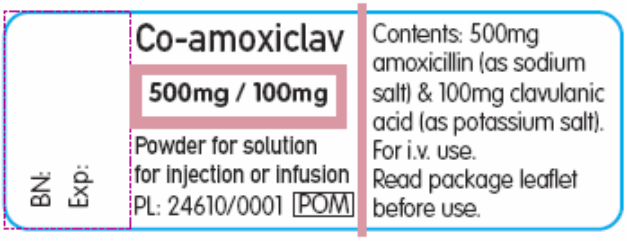
Co-amoxiclav
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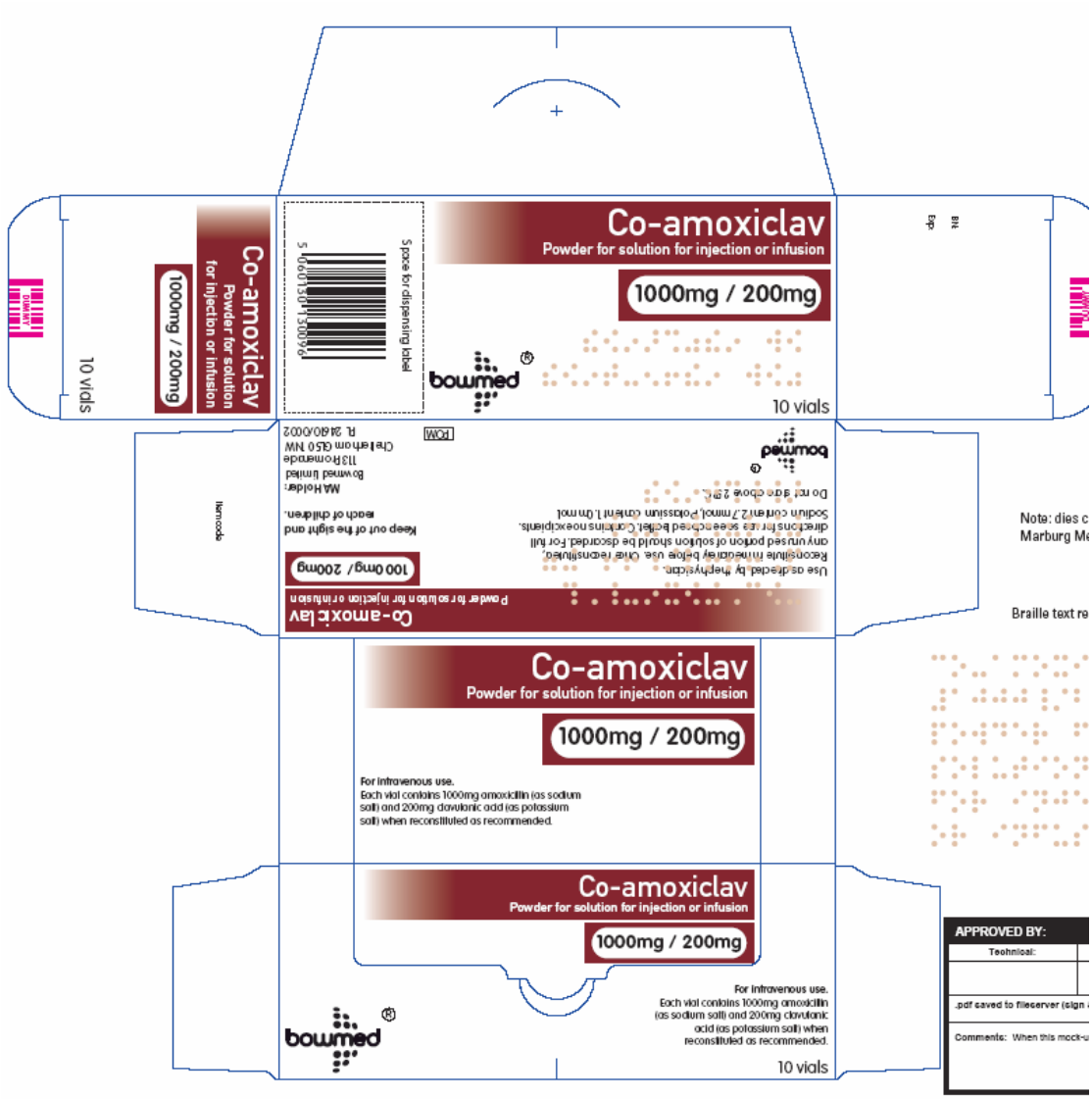
Powder for solution for injection or infusion
PL: 24610/0001
POM
BN:
Exp:
Contents: 500mg amoxicillin (as sodium salt) & 100mg clavulanic acid (as potassium salt).
For i.v. use.
Read package leaflet before use.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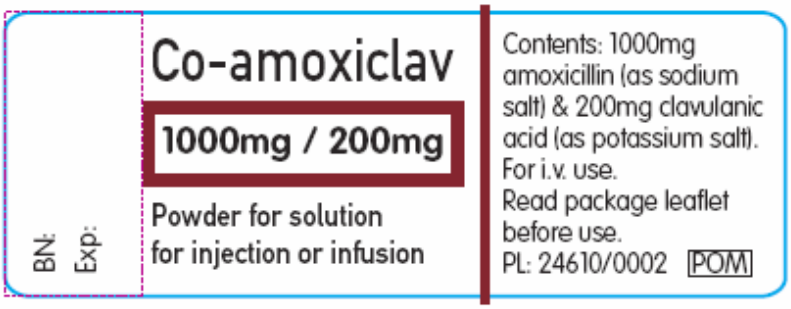
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For i.v. use.
Read package leaflet before use.
PL: 24610/0002
POM