

**CO-AMOXICLAV 500/125MG FILM-COATED TABLETS  
PL 21880/0013**

**UKPAR**

**TABLE OF CONTENTS**

Lay Summary	Page 2
Scientific discussion	Page 3
Steps taken for assessment	Page 14
Steps taken after authorisation – summary	Page 15
Summary of Product Characteristics	
Product Information Leaflet	
Labelling	

## **CO-AMOXICLAV 500/125MG FILM-COATED TABLETS**

### **LAY SUMMARY**

On 17<sup>th</sup> December 2009, the MHRA granted Medreich PLC a Marketing Authorisation (licence) for the medicinal product Co-Amoxiclav 500/125mg Film-Coated Tablets (PL 21880/0013). This is a prescription-only medicine (POM) to treat a wide range of bacterial infections, including those of the chest (bronchitis and pneumonia), tonsils (tonsillitis), sinuses (sinusitis), ears, skin (including animal bites), the bladder or urethra (the tube which carries urine from the bladder), kidneys, abdomen and teeth/gums (abcesses).

This product contains amoxicillin, an antibiotic that belongs to a group called penicillins and clavulanic acid. Amoxicillin works by killing the bacteria that 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 Film-Coated Tablets outweigh the risks. Hence a Marketing Authorisation has been granted.

## **CO-AMOXICLAV 500/125MG FILM-COATED TABLETS**

### **SCIENTIFIC DISCUSSION**

#### **TABLE OF CONTENTS**

Introduction	Page 4
Pharmaceutical assessment	Page 5
Preclinical assessment	Page 8
Clinical assessment (including statistical assessment)	Page 9
Overall conclusions and risk benefit assessment	Page 13

## **INTRODUCTION**

Based on the review of the data on quality, safety and efficacy, the UK granted a Marketing Authorisation for the medicinal product Co-Amoxiclav 500/125mg Film-Coated Tablets (PL 21880/0013) on 17<sup>th</sup> December 2009. The product is for the treatment of bacterial infections induced by gram negative and gram positive amoxicillin-resistant microorganisms whose resistance is caused by  $\beta$ -lactamases which, however, are sensitive to the combination of amoxicillin and clavulanic acid.

This is a standard abridged application for co-amoxiclav film-coated tablets, containing 500mg amoxicillin (as amoxicillin trihydrate) and 125mg clavulanic acid (as potassium clavulanate) submitted under Article 10.1 of Directive 2001/83/EC, as amended. The application claims the product to be a generic medicinal product of Augmentin 625mg Tablets (PL 00038/0362), marketed in the UK by SmithKline Beecham Pharmaceuticals (part of Glaxo SmithKline) since August 1991.

The product contains the active ingredients amoxicillin (as amoxicillin trihydrate) and clavulanic acid (as potassium clavulanate). Amoxicillin is a  $\beta$ -lactam antibiotic, which possesses activity against some gram-positive and gram-negative aerobes and anaerobes. It kills bacteria by inhibiting the bacterial cell-wall synthesis (like all beta-lactam antibiotics). Its action, however, can be inhibited by  $\beta$ -lactamase-producing bacteria strains.

Clavulanic acid is a beta-lactam molecule produced by *Streptomyces clavuligerus*; its beta-lactam ring binds irreversibly to bacterial beta-lactamase thus inactivating this enzyme and preventing its binding to amoxicillin. Clavulanic acid has a high affinity for A beta-lactamases and is also active against chromosomally mediated beta-lactamases. Thus, it protects amoxicillin from inactivation by  $\beta$ -lactamase.

## **PHARMACEUTICAL ASSESSMENT**

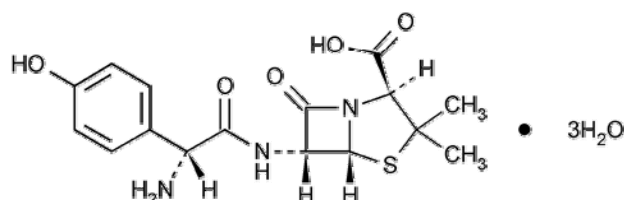
### **ACTIVE SUBSTANCE – AMOXICILLIN TRIHYDRATE**

INN: Amoxicillin trihydrate

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

Molecular Formula:  $C_{16}H_{19}N_3O_5S \cdot 3H_2O$

Chemical Structure:



Molecular Weight: 419.4

Appearance: A white or almost white, crystalline powder

Properties: Very slightly soluble in ethanol and practically insoluble in fatty oils. 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.

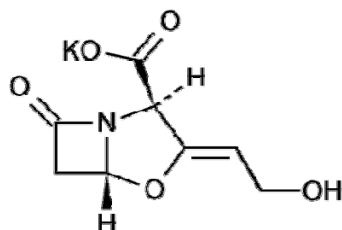
### **ACTIVE SUBSTANCE – POTASSIUM CLAVULANATE**

INN: Potassium clavulanate

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

Molecular Formula:  $C_8H_8KNO_5$

Chemical Structure:



Molecular Weight: 237.3

Appearance: A white or almost white hygroscopic powder

Properties: 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.

## **DRUG PRODUCT**

### **Other ingredients**

Other ingredients consist of pharmaceutical excipients microcrystalline cellulose, croscarmellose sodium, purified talc and magnesium stearate, and a tablet coating (consisting of Opaspray KI-7000 [titanium dioxide and hydroxypropyl cellulose], hypromellose, ethylcellulose and propylene glycol). With the exception of Opaspray KI-7000 and ethylcellulose, all excipients are controlled to their respective British Pharmacopoeia monograph. Opaspray is controlled to a suitable in-house specification and ethylcellulose is controlled to a suitable US Pharmacopoeia specification. Satisfactory certificates of analysis have been provided for all excipients. None of the excipients used contain materials of animal or human origin.

### **Pharmaceutical development**

Suitable pharmaceutical development data have been provided for this application. Comparable dissolution and impurity profile are provided for this product versus the originator product.

### **Manufacture**

A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results appear satisfactory.

### **Finished product specification**

The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

### **Container Closure System**

The finished product is supplied in polyvinylchloride/aluminium blisters in pack sizes of 21 tablets.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with current guidelines concerning materials in contact with food.

### **Stability**

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 24 months has been set, with the storage instructions "Do not store above 25°C. Store in the original package".

**Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and Labelling**

The SPC, PIL and labelling are pharmaceutically satisfactory.

The applicant has submitted results of PIL user testing. The results indicate that the PIL 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.

**MAA Form**

The MAA form is pharmaceutically satisfactory.

**Expert Report**

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

**Conclusion**

It is recommended that a Marketing Authorisation is granted for this application.

## **PRECLINICAL ASSESSMENT**

The pharmacodynamic, pharmacokinetic and toxicological properties of the product are well-known. Thus, the applicant has not provided additional studies and further studies are not required.

A preclinical expert report has been provided, written by an appropriately qualified person. This is satisfactory.

A suitable justification has been provided for non-submission of an environmental risk assessment.



## **CLINICAL ASSESSMENT**

### **TOXICOLOGY**

No new toxicological data have been submitted or are required for this application.

### **CLINICAL PHARMACOLOGY**

#### **Pharmacokinetics**

The following pharmacokinetic study was submitted:

A randomised, single-dose, two-way, two-period, crossover study to assess the pharmacokinetics of the test product Co-Amoxiclav 500/125mg Film-Coated Tablets versus the reference product Augmentin 625mg Tablets (SmithKline Beecham Pharmaceuticals), in healthy fasted volunteers.

Blood samples were taken for pharmacokinetic analysis at pre- and up to 10 hours post dose. Each period was separated by a washout period of 3 days.

A summary of the main pharmacokinetic parameters are presented below:

#### **Amoxicillin**

	<b>Test (mean ± SD)</b>	<b>Reference (mean ± SD)</b>
$C_{\max}$ (µg/mL)	7.594 ± 2.55	7.409 ± 2.42
$AUC_t$ (µg.h/mL)	28.356 ± 7.36	29.167 ± 8.46
$AUC_{\infty}$ (µg.h/mL)	29.875 ± 7.65	30.697 ± 8.46
$T_{\max}$ (h)*	2.24 ± 0.75	2.67 ± 1.28

#### **Clavulanic Acid**

	<b>Test (mean ± SD)</b>	<b>Reference (mean ± SD)</b>
$C_{\max}$ (ng/mL)	665.915 ± 408.83	650.863 ± 383.92
$AUC_t$ (ng.h/mL)	1530 ± 791.52	1474.264 ± 758.64
$AUC_{\infty}$ (ng.h/mL)	1667.490 ± 786.53	1625.227 ± 747.78
$T_{\max}$ (h)*	1.65 ± 0.53	1.72 ± 0.56

Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals:

	<b>Amoxicillin (range)</b>	<b>Clavulanic Acid (range)</b>
$C_{\max}$	1.004 (0.8158-1.2357)	1.036 (0.9245-1.1603)
$AUC_t$	0.964 (0.8341-1.1141)	1.035 (0.9527-1.1215)
$AUC_{\infty}$	0.962 (0.8412-1.1009)	1.020 (0.9504-1.0947)

The 90% confidence intervals for  $AUC_{0-t}$ ,  $C_{\max}$  and  $AUC_{0-inf}$  lie within the acceptance criteria specified by the Committee for Proprietary Medicinal Products (CPMP) Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98). Thus, the test and reference products can be considered to be bioequivalent.

**Pharmacodynamics**

Amoxicillin is a derivative of ampicillin with similar antibacterial spectrum. Amoxicillin kills bacteria by inhibiting the bacterial cell-wall synthesis (like all beta-lactam antibiotics). It is inactivated by beta lactamases and its spectrum of activity is extended by the addition of clavulanic acid, a beta-lactamase inhibitor.

Clavulanic acid is a beta-lactam molecule produced by *Streptomyces clavuligerus*; its beta-lactam ring binds irreversibly to bacterial beta-lactamase thus inactivating this enzyme and preventing its binding to amoxicillin. Clavulanic acid has a high affinity for A beta-lactamases and is also active against chromosomally mediated beta-lactamases.

No new pharmacodynamic data have been submitted or are required for this submission.

**EFFICACY**

No new efficacy data have been submitted or are required for this submission.

**SAFETY**

A total of five adverse events were recorded, none were serious. Two of the adverse events were deemed to be possibly related to the reference product (diarrhoea) and one was considered related with the test product (diarrhoea). All three subjects received concomitant medication to treat their disease.

**EXPERT REPORT**

The Clinical Expert Report has been written by an appropriately qualified person and is a suitable summary of the clinical aspects of the dossier.

**SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**

This is consistent with the SPC for the reference products and is satisfactory.

**PATIENT INFORMATION LEAFLET (PIL)**

The PIL is an accurate reflection of the SPC and complies with the appropriate guidelines.

**LABELLING**

This is satisfactory.

**MAA FORM**

This is satisfactory.

**CONCLUSIONS**

The grant of a Marketing Authorisation is recommended.

## OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

### QUALITY

The important quality characteristics of Co-Amoxiclav 500/125mg 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 benefit/risk balance.

### PRECLINICAL

The preclinical data submitted have not revealed any evidence of potential risks to human health from treatment with Co-Amoxiclav 500/125mg Film-Coated Tablets beyond those already described.

### EFFICACY

No new data have been submitted and none are required for an application of this type.

Co-Amoxiclav 500/125mg Film-Coated Tablets is the generic version of Augmentin 625mg Tablets (SmithKline Beecham Pharmaceuticals). The use of the reference product is well-established in the UK. Both products contain the same quantitative and qualitative composition of the active ingredients, amoxicillin and clavulanic acid.

The 90% confidence intervals for the test/reference lie within the acceptance criteria specified in the CPMP/EWP/QWP/1401/98 *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence*. Bioequivalence of the test product to the reference formulation has been satisfactorily demonstrated in accordance with CHMP criteria.

No new safety data are supplied or required for this generic application. Amoxicillin trihydrate and potassium clavulanate have well-established side-effect profiles and are generally well-tolerated.

The SPC, PIL and labelling are satisfactory.

### BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant's product and the innovator product are interchangeable. Extensive clinical experience with amoxicillin trihydrate and potassium clavulanate is considered to have demonstrated the therapeutic value of the compound. The risk-benefit is, therefore, considered to be positive.

**CO-AMOXICLAV 500/125MG FILM-COATED TABLETS****STEPS TAKEN FOR ASSESMENT**

1	The MHRA received the marketing authorisation applications on 25 <sup>th</sup> August 2005
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 21 <sup>st</sup> September 2005
3	Following assessment of the applications the MHRA requested further information on 9 <sup>th</sup> February 2006 for the clinical parts of the dossier and on 20 <sup>th</sup> February 2006, 1 <sup>st</sup> June 2007, 21 <sup>st</sup> January 2008, 26 <sup>th</sup> September 2008, 15 <sup>th</sup> June 2009 and 11 <sup>th</sup> September 2009 for the pharmaceutical parts of the dossier
4	The applicant responded to the MHRA's requests, providing further information on 7 <sup>th</sup> January 2007 for the clinical sections, and again on 7 <sup>th</sup> January 2007, 27 <sup>th</sup> July 2007, 28 <sup>th</sup> February 2008, 29 <sup>th</sup> January 2009, 24 <sup>th</sup> June 2009 and 17 <sup>th</sup> December 2009 for the quality sections.
5	The applications were determined on 17 <sup>th</sup> December 2009

**CO-AMOXICLAV 500/125MG FILM-COATED TABLETS****STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

<b>Date submitted</b>	<b>Application type</b>	<b>Scope</b>	<b>Outcome</b>

**1 NAME OF THE MEDICINAL PRODUCT**

Co-amoxiclav 500mg/125mg Film-Coated Tablets

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film coated tablet contains 575mg amoxicillin trihydrate equivalent to 500mg amoxicillin and 148.875mg potassium clavulanate equivalent to 125mg Clavulanic acid

For a full list of excipients, see section 6.1.

**3 PHARMACEUTICAL FORM**

Film-coated tablet

Co-Amoxiclav 500mg/125mg Film-coated Tablets are presented as White, oval, film-coated tablets, with the markings "CA 625" on one face.

**4 CLINICAL PARTICULARS****4.1 Therapeutic indications**

Treatment of bacterial infections induced by gram negative and gram positive amoxicillin-resistant microorganisms whose resistance is caused by  $\beta$ -lactamases which however are sensitive to the combination of amoxicillin and clavulanic acid.

Co-amoxiclav 500mg/125mg Tablets are suitable for treatment of the following indications when known or likely to be due to susceptible organisms (see section 5.1):

- Infections of the upper respiratory tract Infections (including ear-nose-throat) in particular sinusitis, otitis media, recurrent tonsillitis.
- Infections of the lower respiratory tract, in particular acute exacerbations of chronic bronchitis and bronchopneumonia.
- Genital and urinary tract infections.
- Infections of the skin and soft tissues.

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

**4.2 Posology and method of administration**

Usual dosages for the treatment of infection

*Adults and children over 12 years:*

One Co-amoxiclav 500mg/125mg Tablets three times a day.

*Children:*

Co-amoxiclav 500mg/125mg Tablets are not recommended in children of 12 years and under.

*Administration*

*Oral:* Tablets. To minimise potential gastrointestinal intolerance, administer at the start of a meal. The absorption of Co-amoxiclav is optimised when taken at the start of a meal.

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

***Renal impairment***

It may be necessary to reduce the total daily dosage depending on the degree of renal impairment.

*Mild impairment (creatinine clearance >30 ml/min):* No change in dosage.

*Moderate impairment (creatinine clearance 10-30 ml/min):* One 625 mg tablet 12 hourly.

*Severe impairment (creatinine clearance <10 ml/min):* Not recommended.

Patients receiving haemodialysis may require another dose of co-amoxiclav at the end of their dialysis.

#### ***Hepatic impairment***

Dose with caution; monitor hepatic function at regular intervals.

There are, as yet, insufficient data on which to base a dosage recommendation.

### **4.3 Contraindications**

Penicillin hypersensitivity. Attention should be paid to possible cross-sensitivity with other  $\beta$ -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**

Mixed infections caused by organisms susceptible to amoxicillin and beta-lactamase-producing –organisms susceptible to amoxicillin/clavulanic acid and do not usually require the addition of another beta-lactam antibiotic.

The therapy should only be applied with caution in patients with pre-existing hepatic impairment. Caution is necessary on treatment of patients with high-grade hepatic functional impairment and in older patients (60 years and older): liver function tests are indicated in such patients (see section 4.8).

In case of severe and persistent diarrhoea, the possibility of pseudomembranous colitis caused by *Clostridium difficile* must be considered and amoxicillin/clavulanic acid therapy must not be continued. Antiperistaltics are contraindicated.

Co-amoxiclav 500mg/125mg Tablets should be used with caution in patients with severe allergies or asthma since such patients are more likely to respond with allergic reactions.

Before initiating therapy careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other substances. Serious and occasionally fatal hypersensitivity reactions have been reported in patients with a history of penicillin hypersensitivity.

Erythematous rashes have been associated with glandular fever in patients receiving amoxicillin.

Amoxicillin may precipitate in the bladder catheter if present in urine at high concentrations at room temperature, therefore the catheter should be checked at regular intervals in such cases.

On long-term-use the same as with other broad-spectrum-antibiotics-superinfections with resistant bacteria or yeasts are possible.

Regular checks on renal and hepatic function and haematological studies are indicated during long term treatment.

### **4.5 Interaction with other medicinal products and other forms of interaction**

#### **Amoxicillin/clavulanic acid and other antibiotics or chemotherapeutics**

Co-amoxiclav 500mg/125mg Tablets should not be combined with bacteriostatic chemotherapeutics/antibiotics (such as tetracyclines, macrolides, sulphonamides or chloramphenicol) since an antagonistic effect has been observed in vitro.

#### **Amoxicillin/clavulanic acid and probenecid**

Concomitant administration of probenecid leads to an increase in and prolongation of serum and bile amoxicillin concentration owing to inhibition of renal excretion. However this does not affect the excretion of clavulanic acid.

Amoxicillin/clavulanic acid and allopurinol

Concomitant administration of allopurinol during therapy with Co-amoxiclav 500mg/125mg Tablets may promote the occurrence of allergic cutaneous reactions (exanthema).

Amoxicillin/clavulanic acid and sulfasalazin

Aminopenicillin may reduce the plasmatic concentration of sulfasalazin.

Amoxicillin/clavulanic acid and methotrexate

Interaction between amoxicillin and methotrexate leading to methotrexate toxicity has been reported. Serum methotrexate levels should be closely monitored in patients who receive concomitant amoxicillin. Amoxicillin decreases the renal clearance of methotrexate probably by competition at the common tubular secretion system.

Amoxicillin/clavulanic acid and digoxin

An increase in absorption of digoxin is possible on concurrent administration with Co-amoxiclav 500mg/125mg Tablets

Amoxicillin/clavulanic acid and anticoagulants

A tendency to bleed can be potentiated due to concomitant administration of Co-amoxiclav 500mg/125mg Tablets and anticoagulants of the coumarin class.

Amoxicillin/clavulanic acid and hormonal contraceptives

In rare cases amoxicillin can adversely affect the efficacy of hormonal contraceptives. Supplementary non-hormonal contraceptive measures should be taken.

Amoxicillin/clavulanic acid and disulfiram

Co-amoxiclav should not be used concomitantly with disulfiram

Influence on results of diagnostic laboratory tests

Nonenzymic methods for determining urinary sugar can yield falsely positive results. Likewise the urobilinogen test can be affected.

#### **4.6 Pregnancy and lactation**

*Pregnancy*

Data on a limited number (560) of exposed pregnancies indicate no adverse effects of amoxicillin/clavulanic acid on pregnancy or on the health of the foetus/newborn child. A single study in women with premature rupture of the amnion reported that prophylactic treatment with amoxicillin/clavulanic acid can be associated with an increased risk of necrotising enterocolitis in neonates.

To date no other relevant epidemiological data are available. Caution should be exercised when prescribing to pregnant women.

*Lactation*

Amoxicillin/clavulanic acid can be used during breastfeeding. Amoxicillin/clavulanic acid is excreted in human milk but no effects have been shown in breastfed newborns/infants of treated mothers. However there is a risk of sensitisation associated with the excretion of trace quantities of breast milk.

#### **4.7 Effects on ability to drive and use machines**

Amoxicillin/clavulanic acid has a minor or moderate influence on the ability to drive and use machines. Amoxicillin/clavulanic acid may sometimes be associated with adverse reactions such as mental confusion, rarely dizziness and even less often convulsions that may impair the ability to drive a vehicle, to operate machines and/or to work safely (see section 4.8).



#### 4.8 Undesirable effects

Approximately 5% of patients can be expected to experience adverse reactions.

Gastrointestinal disorders with loose stools, nausea and vomiting occur more frequently at higher doses and have been reported more frequently compared to treatment with amoxicillin alone.

Common ( $>1/100$  to  $<1/10$ )

Uncommon ( $>1/1,000$  to  $<1/100$ )

Rare ( $>1/10,000$  to  $<1/1,000$ )

Very rare ( $<1/10,000$ )

##### *Infections and infestations*

###### *Uncommon*

Prolonged and repeated use of the preparation can result in superinfections and colonisation with resistant organisms or yeasts.

##### *Blood and the lymphatic system disorders*

###### *Rare*

Thrombocytosis, haemolytic anaemia

###### *Very rare*

Changes in blood count in form of leucopenia, agranulocytosis, thrombocytopenia, pancytopenia, anaemia or myelosuppression and prolongation of the bleeding and prothrombin time have been observed in isolated cases. These manifestations are reversible after discontinuation of therapy.

##### *Immune system disorders*

###### *Rare*

Typical type I allergic reactions (such as urticaria, purpura), angio-oedema and anaphylaxis can occur less frequently.

Erythema multiforme, Lyell syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalised erythematous pustulosis, bullous exfoliative dermatitis, serum sickness and vasculitis associated with hypersensitivity rarely occur.

Drug fever.

##### *Psychiatric disorders*

###### *Very rare*

Hyperactivity, anxiety, sleeplessness, mental confusion and aggression.

##### *Nervous system disorders*

###### *Rare*

Dizziness, headache and convulsions are rare. Convulsions may occur with impaired renal function or in those receiving high doses.

##### *Gastrointestinal disorders*

###### *Common*

Gastro-intestinal disturbances such as nausea, vomiting and diarrhoea and pruritis ani have been observed. These side effects are generally of a mild and transitory nature.

###### *Rare*

Pseudomembranous colitis, haemorrhagic colitis, mucocutaneous candidiasis, superficial tooth discolouration.

###### *Very rare*

Development of a black tongue.

A single study in women with premature rupture of the amnion reported that prophylactic treatment with amoxicillin/clavulanic acid can be associated with an increased risk of necrotising enterocolitis in neonates.

*Hepato-biliary disorders**Rare*

In rare cases a moderate rise in AST and/or ALT values has been reported.

*Very rare*

Hepatitis and cholestatic jaundice have been reported rarely. Hepatic events occur predominantly in males and elderly patients, particularly those over 60 years of age. The risk of these events occurring increases with treatment for more than 14 days.

These side effects are very rarely reported in children.

Signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until some weeks after treatment has ceased. Hepatic events are usually transient. However they may be severe and in very rare cases a fatal outcome has been reported. These have mostly occurred in patients with a serious underlying disease, or patients taking potentially hepatotoxic agents in addition to amoxicillin/clavulanic acid.

*Skin and subcutaneous tissue disorders**Common*

Allergic skin reactions occur significantly more often than with other penicillins and generally are maculopapular in nature.

In some cases 'fifth day rash' (a morbilliform exanthema) is reported. This is dependent on the size of the dose and the patient's condition.

*Renal and urinary disorders**Very rare*

Interstitial nephritis has occurred on a single occasion. Crystalluria has been reported.

*Reproductive system and breast disorders**Uncommon*

Vaginal itching and discharge.

**4.9 Overdose**

In case of overdosage, gastrointestinal symptoms such as nausea, vomiting and diarrhoea and disturbances of the fluid and electrolyte balance are possible. Also convulsions may exist. Reduced level of consciousness, muscle fasciculations, myoclonic jerks, coma, haemolytic reactions, renal failure and acidosis are possible. Shock can occur within 20 to 40 minutes in exceptional circumstances.

There is no specific antidote to an overdose. Treatment consists of haemodialysis and symptomatic measures paying attention to water and electrolyte balance. Administration of medicinal charcoal and gastric lavage are useful only in cases of very high overdose.

**5 PHARMACOLOGICAL PROPERTIES****5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors; ATC code: J01CR02

Mode of action

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) 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.

Amoxicillin is susceptible to degradation by beta-lactamases manufactured by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a beta-lactam agent structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

#### PK/PD relationship

The time above the minimum inhibitory concentration ( $T > MIC$ ) is considered to be the major determinant of efficacy for amoxicillin.  $T > MIC$  should be  $\geq 40\%$  during the interval of administration.

#### Mechanisms of resistance

The two main mechanisms of resistance to beta-lactam antibacterial agents are:

- Inactivation by bacterial beta-lactamases.
- Alteration of the penicillin-binding proteins that reduce the affinity of the antibacterial agent for the target.

Less often impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance.

#### Breakpoints

MIC breakpoints for Co-amoxiclav are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Organism	Susceptibility Breakpoints ( $\mu\text{g/ml}$ )		
	Susceptible	Intermediate	Resistant
<i>Haemophilus influenzae</i> <sup>1</sup>	$\leq 1$	-	$> 1$
<i>Moraxella catharrhalis</i> <sup>1</sup>	$\leq 1$	-	$> 1$
<i>Staphylococcus aureus</i> <sup>2</sup>	$\leq 2$	-	$> 2$
Coagulase-negative staphylococci <sup>2</sup>	$\leq 0.25$		$> 0.25$
<i>Enterococcus</i> <sup>1</sup>	$\leq 4$	8	$> 8$
<i>Streptococcus A, B, C, G</i> <sup>5</sup>	$\leq 0.25$	-	$> 0.25$
<i>Streptococcus pneumoniae</i> <sup>3</sup>	$\leq 0.5$	1-2	$> 2$
Enterobacteriaceae <sup>1,4</sup>	-	-	$> 8$
Gram-negative anaerobes <sup>1</sup>	$\leq 4$	8	$> 8$
Gram-positive Anaerobes <sup>1</sup>	$\leq 4$	8	$> 8$
Non-species related breakpoints <sup>1</sup>	$\leq 2$	4-8	$> 8$
<sup>1</sup> The reported values are for Amoxicillin concentrations. For susceptibility testing purposes, the concentration of clavulanic acid is fixed at 2 mg/l. <sup>2</sup> The reported values are Oxacillin-values. <sup>3</sup> Breakpoint values in the table are based on ampicillin breakpoints. <sup>4</sup> The resistant breakpoint of $R > 8$ mg/L ensures that all isolates with resistance mechanisms are reported resistant. <sup>5</sup> Breakpoint values in the table are based on Benzylpenicillin breakpoints.			

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.

<u>Commonly susceptible species</u>
<u>Aerobic Gram-positive micro-organisms</u> <i>Enterococcus faecalis</i> <i>Staphylococcus aureus</i> (methicillin-susceptible)† <i>Streptococcus agalactiae</i> <i>Streptococcus pneumoniae</i> * <i>Streptococcus pyogenes</i> * and other beta-hemolytic streptococci <i>Streptococcus viridans</i> group

<u>Aerobic Gram-negative micro-organisms</u> <i>Capnocytophaga</i> spp. <i>Eikenella corrodens</i> <i>Moraxella catarrhalis</i> * <i>Pasteurella multocida</i>  <u>Anaerobic micro-organisms</u> <i>Bacteroides fragilis</i> <i>Fusobacterium nucleatum</i> <i>Prevotella</i> spp.
<u>Species for which acquired resistance may be a problem</u>
<u>Aerobic Gram-positive micro-organisms</u> <i>Enterococcus faecium</i> §  <u>Aerobic Gram-negative micro-organisms</u> <i>Escherichia coli</i> <i>Haemophilus influenzae</i> * <i>Klebsiella oxytoca</i> <i>Klebsiella pneumoniae</i> <i>Proteus mirabilis</i> <i>Proteus vulgaris</i>
<u>Inherently resistant organisms</u>
<u>Aerobic Gram-negative micro-organisms</u> <i>Acinetobacter</i> spp. <i>Citrobacter freundii</i> <i>Enterobacter</i> sp. <i>Legionella pneumophila</i> <i>Morganella morganii</i> <i>Providencia</i> spp. <i>Pseudomonas</i> sp. <i>Serratia</i> sp. <i>Stenotrophomonas maltophilia</i>  <u>Other micro-organisms</u> <i>Chlamydophila pneumoniae</i> <i>Chlamydophila psittaci</i> <i>Coxiella burnetii</i> <i>Mycoplasma pneumoniae</i>

\* Clinical effectiveness has been demonstrated for susceptible isolates in approved clinical indications.

§ Natural intermediate susceptibility in the absence of acquired mechanism of resistance.

£ All methicillin-resistant staphylococci are resistant to co-amoxiclav

## 5.2 Pharmacokinetic properties

Amoxicillin:

The absolute bioavailability of amoxicillin depends on the dose and ranges between approximately 72 and 94%. Absorption is not affected by intake of food. Plasma concentrations are present about 1 to 2 hours after administration of amoxicillin. The apparent distribution volume ranges between approximately 0.3 and 0.4 l/kg and binding to serum proteins is approximately 17-20%. Amoxicillin diffuses through the placental barrier and a small fraction is excreted into breast milk.

Amoxicillin is largely excreted through the kidneys ( $52 \pm 15\%$  of a dose in unchanged form within 7 hours) and a small fraction is excreted in the bile. Total clearance ranges between approximately 250 and 370 ml/min. The serum half-life of amoxicillin in subjects with intact renal function is approximately 1 hour (0.9 – 1.2h), in patients with creatinine clearance ranging between 10 and 30 ml/min it is about 6 hours and in anuria it ranges between 10 and 15 hours.

**Clavulanic acid:**

The absolute bioavailability of clavulanic acid of approximately 60% differs markedly from individual to individual. Peak concentrations of clavulanic acid are present after approximately 1 to 2 hours. The apparent distribution volume is about 0.2 l/kg and the serum protein binding rate is approximately 22%. Clavulanic acid diffuses through the placental barrier. No exact data are as yet available in regard to excretion into breast milk.

The substance is partly metabolised (approximately 50 – 70%) and about 40% is eliminated through the kidneys (18-38% of the dose in unchanged form). The total clearance is approximately 260 ml/min. The serum half-life of clavulanic acid in subjects with intact renal function is approximately 1 hour, in patients with creatinine clearance ranging between 20 and 70 ml/min it is approximately 2.6 hours and in anuria it ranges between 3 and 4 hours.

Pharmacologically relevant pharmacokinetic interactions between amoxicillin and clavulanic acid have not been observed so far.

Both amoxicillin and clavulanic acid are haemodialysable.

**5.3 Preclinical safety data****a) Acute toxicity**

The LD50 of clavulanic acid (potassium salt) is determined by the potassium content. Administration of clavulanic acid (potassium salt) together with amoxicillin does not result in any unexpected or synergistic toxicity.

**b) Chronic toxicity/subchronic toxicity**

The animal species used in chronic toxicity studies were rats and dogs.

Solely after high doses (corresponding to 20- to 50-fold the maximal human dose) were mild haematological and blood-chemical changes observed, which regressed completely following discontinuation of therapy.

**c) 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.

**d) Reproduction toxicity**

Reproduction toxicity studies in rats did not show any adverse effects of the combination on fertility and no teratogenic effects were evident. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, strength of contractions and duration of contractions. The relevance of these findings in humans is unknown.

**6 PHARMACEUTICAL PARTICULARS****6.1 List of excipients**

Each tablet contains:

Tablet Core:

Microcrystalline cellulose

Croscarmellose sodium

Purified talc

Magnesium stearate

Tablet Coating:

Opaspray KI-7000 (Contains: Titanium Dioxide (E171) and hydroxypropyl cellulose (E463))

Hypromellose (E464)

Ethylcellulose

Propylene glycol

**6.2 Incompatibilities**

Not applicable

- 6.3 Shelf life**  
24 months.  
Once a foil pouch has been opened, use enclosed tablets within 7 days.
- 6.4 Special precautions for storage**  
Do not store above 25°C. Store in the original packaging.
- 6.5 Nature and contents of container**  
PVC/Aluminium blister packs. Each blister of 7 tablets is enclosed within an aluminium pouch. Three pouches are packaged into cartons. Each pack contains 21 tablets.
- 6.6 Special precautions for disposal**  
No special requirements.
- 7 MARKETING AUTHORISATION HOLDER**  
Medreich PLC  
9 Royal Parade,  
Kew Gardens,  
London,  
TW9 3QD.
- 8 MARKETING AUTHORISATION NUMBER(S)**  
PL 21880/0013
- 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**  
17/12/2009
- 10 DATE OF REVISION OF THE TEXT**  
17/12/2009



#### 5. How to Store Co-amoxiclav 500 mg/125 mg Tablets

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

Do not store above 25 °C.

Store in the original packaging.

Keep all medicines out of the reach and sight of children.

If your doctor tells you to stop taking this medicine, or for any reason you have some tablets left over, please return them to your pharmacist.

Once a full pouch has been opened, use enclosed tablets within 7 days.

#### 6. Further information

##### What Co-amoxiclav 500 mg/125 mg Tablets contain

Co-amoxiclav 500 mg/125 mg Tablets contain 575.0 mg amoxicillin trihydrate equivalent to 500 mg amoxicillin and 148.875 mg potassium clavulanate equivalent to 125 mg clavulanic acid.

Both of these ingredients are antibiotics and together they are known as co-amoxiclav.

**Tablet core:-** microcrystalline cellulose, croscarmellose sodium, purified talc, magnesium stearate

**Tablet coating:-** Opaspray KI-7000, hypromellose, ethylcellulose, propylene glycol.

##### What Co-amoxiclav 500 mg/125 mg Tablets look like and contents of the pack.

Co-amoxiclav 500 mg/125 mg Tablets are white, oval-shaped film coated tablets with CA625 on one face which are supplied in foil pouches in packs of 21 tablets.

PL No.: 21880/0013

POM

Date of leaflet preparation: June 2009

MA Holder & Manufacturer:  
**MEDREICH plc**  
9, Royal Parade, Kew Gardens,  
Surrey TW9 3QD, England.

4

1206644



#### 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 further questions, please 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 pharmacist.

##### In this leaflet:

1. What Co-amoxiclav 500 mg/125 mg Tablets are and what they are used for
2. Before you take Co-amoxiclav 500 mg/125 mg Tablets
3. How to take Co-amoxiclav 500 mg/125 mg Tablets
4. Possible side effects
5. How to store Co-amoxiclav 500 mg/125 mg Tablets
6. Further information.

##### 1. What Co-amoxiclav 500 mg/125 mg Tablets are and what they are used for?

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

Amoxicillin can treat a wide range of bacterial infections including those of the chest (bronchitis or pneumonia), tonsils (tonsillitis), sinuses (sinusitis), ears, skin (including animal bites), the bladder or urethra (the tube which carries urine from the bladder), kidneys, abdomen and teeth and gums (abscesses).

##### 2. Before you take Co-amoxiclav 500 mg/125 mg Tablets

###### Do not take Co-amoxiclav 500 mg/125 mg Tablets

- If you are allergic (hypersensitive) to amoxicillin or clavulanic acid or any of the ingredients of this product with symptoms of a skin rash or swelling of the face or neck or difficulty breathing.
- If you have a history of being allergic to penicillin or other-lactam antibiotics e.g. cephalosporins.
- If you have had a history of penicillin associated jaundice (with yellowing of the eyes and skin) or liver problems.

##### Take special care with Co-amoxiclav 500 mg/125 mg Tablets

Tell your doctor before taking these tablets:-

- If you have liver or kidney problems.
- If you are elderly as your kidney and liver function may be impaired, in which case your doctor may have a blood test done first to check this.
- If you have severe diarrhoea.
- If you have asthma.
- If you have a catheter.
- If you are on antibiotics for a long time as blood tests may be necessary to monitor your liver and kidney function and your blood cell counts.

##### Taking other medicines

Please tell your doctor if you are taking or have recently taken other medicines, including medicines without a prescription.

Please tell your doctor if you are taking any of the following medicines:-

- Other antibiotics e.g. chloramphenicol
- Medicines used to treat gout e.g. allopurinol, probenecid
- Medicines used to treat Crohn's disease or rheumatoid arthritis

1





e.g. *sulfasalazine, methotrexate*

- Medicines to prevent blood clotting e.g. *warfarin*
- *Digoxin* used to treat heart problems
- Oral contraceptive pill
- *Disulfiram* used in the treatment of chronic alcohol dependence

Inform your doctor if you are on these tablets and you are having a blood test as they may interfere with some blood test results

#### **Taking Co-amoxiclav 500 mg/125 mg Tablets with food and drink**

You should swallow the tablets whole with water. For the best results take these tablets just before meals.

#### **Pregnancy and breast-feeding**

As with all medicines, if you are pregnant or breast-feeding you should consult your doctor before using Co-amoxiclav 500 mg/125 mg Tablets. Your doctor will decide if it is safe for you to use Co-amoxiclav 500 mg /125 mg Tablets.

#### **Driving and using machines**

Most people taking Co-amoxiclav 500 mg/125 mg Tablets are able to safely drive and operate machines, however occasionally the medicine may cause confusion and dizziness. If you experience these symptoms, do not drive or operate machines, and consult your doctor.

### **3. How to take Co-amoxiclav 500 mg/125 mg Tablets**

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

The usual dose for:-

#### **Adults and children over 12 years old**

One Co-amoxiclav 500 mg/125 mg tablet to be taken three times a day.

#### **Patients with reduced kidney function**

Your doctor may reduce the total daily dosage depending on the level of kidney function.

#### **Children**

These tablets are not recommended for children 12 years and younger.

#### **Elderly**

The doctor may reduce the daily dose for older patients (60 years or older) who may have reduced kidney function.

Your doctor will tell you how many tablets you should take. Usually you have to take one tablet three times a day. Your doctor's instructions are on the label of the tablets container, so read it carefully. If you have any questions, talk to your doctor or pharmacist.

**If you take more Co-amoxiclav 500 mg/125 mg Tablets than you should** contact your doctor or local hospital casualty department at once. Show the doctor your pack of tablets. Signs of overdose include nausea, sickness and diarrhoea, which may then be followed by sleepiness and fitting.

**If you forget to take Co-amoxiclav 500 mg/125 mg Tablets**, take it as soon as you remember. Then carry on as before. Try to wait for four hours before taking the next dose. Do not take two doses within an hour or so.

### **4. POSSIBLE SIDE EFFECTS**

Like all medicines Co-amoxiclav 500 mg/125 mg Tablets can cause side effects, although not everyone gets them.

An allergic (hypersensitive) reaction may occur whilst taking Co-amoxiclav tablets. If you develop any of the following reactions, tell

2

1206944



your doctor immediately.

- Sudden wheezing, difficulty breathing, tightness in the chest
- Swelling of the eyelids, face or lips
- Skin lumps or red itchy spots
- An itch all over your body
- A serious allergic reaction may result in inflammation of the kidneys

You may have a serious but rare reaction resulting in Severe diarrhoea with bleeding

Notice your urine becoming darker or your faeces (otherwise known as poo) becoming paler

Notice your skin or whites of your eyes turning yellow

Other side effects are:-

Common (greater than 1/100 to less than 1/10 patients)

#### Gastrointestinal disorders

- Nausea, vomiting, diarrhoea

These symptoms should disappear quickly and can be helped by taking the tablets with food.

Uncommon (greater than 1/1000 to less than 1/100 patients)

#### Infections and infestations:

- Prolonged use can result in superinfections

#### Reproductive system and breast disorders

- Vaginal itching and discharge

Rare (greater than 1/10,000 to 1/1000 patients)

#### Blood and lymphatic system disorders

- Abnormally high or low red blood cell counts (measured by a blood test)

#### Immune system disorder

- Drug fever
- Inflammation of the skin

#### Nervous system disorders

- Dizziness, headache and convulsions especially with those with kidney problems

#### Gastrointestinal disorders

- Superficial tooth discolouration

#### Hepatobiliary disorders

- A rise in some liver enzymes measured by a blood test

If these side effects occur contact your doctor or pharmacist for advice.

Very Rare (less than 1/10,000 patients)

#### Blood and lymphatic system disorders

- Changes in some blood cell counts (measured by a blood test)

#### Psychiatric disorder

- Restlessness, anxiety, sleeplessness, mental confusion and aggression

#### Gastrointestinal disorders

- Development of a black tongue

#### Renal and urinary disorders

- This medicine may form crystals in the urine giving it a cloudy appearance

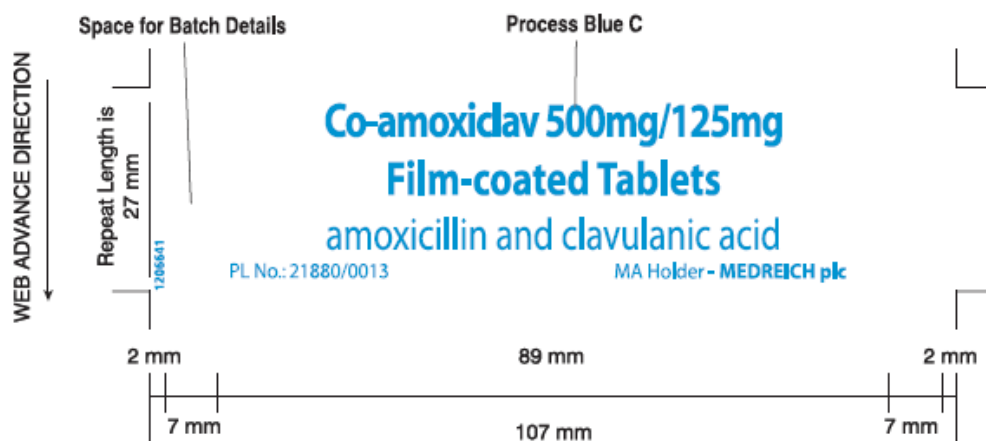
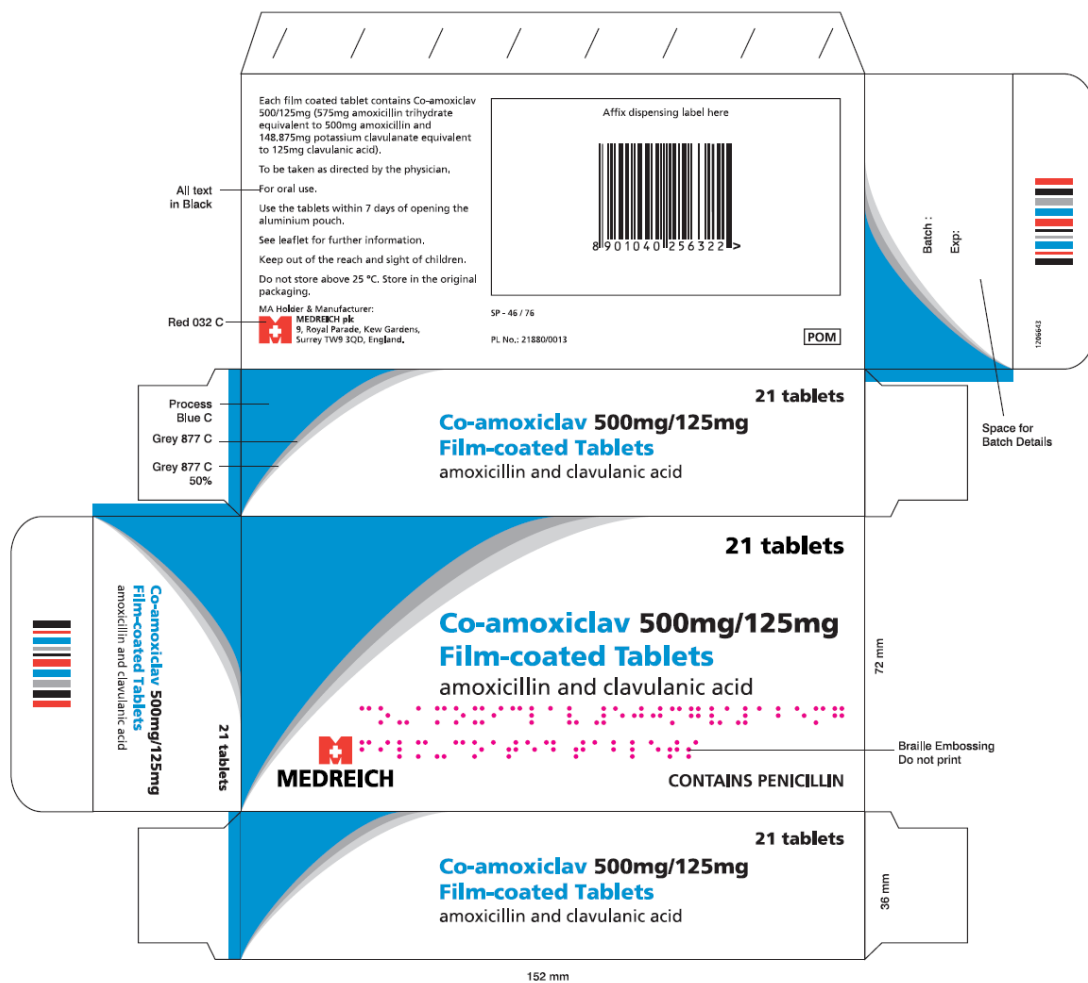
If these side effects occur contact your doctor immediately.

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

3







**Co-amoxiclav 500mg/125mg**  
**Film-coated Tablets**  
amoxicillin and clavulanic acid

PL No.: 21880/0013

MA Holder - **MEDREICH plc**

1206641



MEDREICH plc

**Co-amoxiclav 500mg/125 mg**  
**Film-coated Tablets**

amoxicillin and clavulanic acid  
7 Tablets  
For oral administration



MEDREICH plc

**Co-amoxiclav 500mg/125 mg**  
**Film-coated Tablets**

amoxicillin and clavulanic acid  
7 Tablets  
For oral administration



MEDREICH plc

**Co-amoxiclav 500mg/125 mg**  
**Film-coated Tablets**

amoxicillin and clavulanic acid  
7 Tablets  
For oral administration

PL No.: 21880/0013

Use the tablets within 7 days of opening the pouch

Keep out of the reach and sight of children

Contains Penicillin. Do not store above 25 °C. Store in the original packaging.

140 mm

150 mm

Reflex Blue C

Space For  
Batch Details