# CO-AMOXICLAV 457MG/5ML SUSPENSION (PL 21880/0011)

# UKPAR

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# CO-AMOXICLAV 457MG/5ML SUSPENSION (PL 21880/0011)

## LAY SUMMARY

On 29th June 2009, the MHRA granted Medreich PLC a Marketing Authorisation (licence) for the medicinal product Co-Amoxiclav 457/5ml Suspension (PL 21880/0011). This is a prescription-only medicine (POM) for the treatment of certain types of bacterial infection.

Co-Amoxiclav Oral Suspension is an antibiotic for treating infections. It belongs to a group of antibiotics called penicillins. Co-Amoxiclav Oral Suspension works by killing the bacteria that cause infections and can 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 that carries urine from the bladder), kidneys, and teeth and gums.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Co-Amoxiclav Oral Suspension outweigh the risks, hence a Marketing Authorisation has been granted.

# CO-AMOXICLAV 457MG/5ML SUSPENSION (PL 21880/0011)

## SCIENTIFIC DISCUSSION

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# 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 457/5ml Suspension (PL 21880/0011) to Medreich PLC on 29th June 2009. The products are prescription-only medicines for the treatment of bacterial infections induced by gram-negative and gram-positive amoxicillin-resistant microorganisms, whose resistance is caused by β-lactamases which are sensitive to the combination of amoxicillin and clavulanic acid.

This is a standard abridged application for co-amoxiclav powder for reconstitution into oral suspension (containing 400mg amoxicillin and 57mg clavulanic acid per 5 ml) submitted under Article 10.1 of Directive 2001/83/EC as amended. The application claims to be a generic medicinal product of Augmentin Duo 400/57 (PL 10592/0070), marketed in the UK by SmithKline Beecham (part of Glaxo SmithKline) since 1995.

The product contains the active ingredients amoxicillin (as amoxicillin trihydrate) and clavulanic acid (as potassium clavulanate). Amoxicillin is a β-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 β-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 β-lactamase.

# PHARMACEUTICAL ASSESSMENT

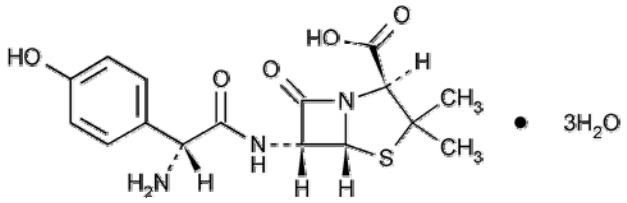
## ACTIVE SUBSTANCE – AMOXICILLIN TRIHYDRATE

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.

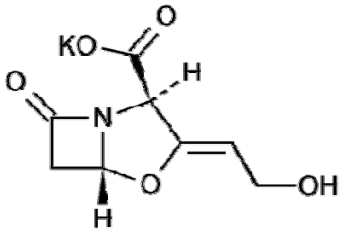
## ACTIVE SUBSTANCE – POTASSIUM CLAVULANATE

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, namely xanthan gum (E415), aspartame (E951), silicon dioxide (E551), colloidal silica, anhydrous citric acid, hypromellose, flavour orange dry powder, flavour raspberry dry powder and flavour golden dry powder. With the exception of silicon dioxide and the three flavourings, all excipients are controlled to their respective European Pharmacopoeia specifications. Silicon dioxide is controlled to a US Pharmacopoeia monograph and the flavours are controlled to suitable in-house specifications.

Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contain materials of animal or human origin.

### Pharmaceutical development

The objective of the product development programme was to produce a powder for suspension that could be considered a generic medicinal product of Augmentin Duo 400/57 (PL 10592/0070).

The pharmaceutical development data submitted are satisfactory.

### Manufacture

A description and flow-chart of the manufacturing method has 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 product. The results appear satisfactory.

### Finished product specification

The finished product specification is satisfactory. Test methods have been described and have been 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 packaged in107ml glass, round shaped bottles, containing an off-white dry powder. The bottle is fitted with a polypropylene child-resistant cap and packed in cartons with a 30ml measuring cup with 2.5ml graduations.

Specifications and Certificates of Analysis for all packaging have been provided. These are satisfactory. The primary packaging has been shown to comply with relevant regulations regarding the contact of materials with foodstuff.

### Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set for the powder and

7 days for the reconstituted suspension. Storage conditions are “Do not store above 25°C. Keep the bottle tightly closed” for the dry powder and “Store at 2-8°C. Do not freeze” for the reconstituted solution.

## ADMINISTRATIVE

### Expert Report

A pharmaceutical expert report has been written by a suitably qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

### Summary of Product Characteristics (SPC)

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

### Labelling

These are satisfactory.

### Patient Information Leaflet (PIL)

This is consistent with the PIL for the reference product and is satisfactory.

### MAA Form

This is satisfactory.

### Conclusion

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

# PRECLINICAL ASSESSMENT

These applications for generic products claims essential similarity to Augmentin Duo 400/57 (PL 10592/0070), marketed in the UK by SmithKline Beecham (part of Glaxo SmithKline) since 1995.

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

# 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 457mg/5ml Suspension versus the reference product Augmentin 475mg/5ml Oral Suspension (Smithkline Beecham), 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**

| | **Test (mean ± SD)** | **Reference (mean ± SD)** |
|---|---|---|
| $C_{max}$ (µg/mL) | 11.772 ± 4.01 | 11.560 ± 3.24 |
| $AUC_t$ (µg.h/mL) | 41.958 ± 13.42 | 41.712 ± 10.82 |
| $AUC_\infty$ (µg.h/mL) | 43.719 ± 14.21 | 43.270 ± 11.34 |
| $T_{max}$ (h)* | 1.76 ± 0.63 | 1.92 ± 0.60 |

**Clavulanic Acid**

| | **Test (mean ± SD)** | **Reference (mean ± SD)** |
|---|---|---|
| $C_{max}$ (ng/mL) | 1233.001 ± 560.58 | 1215.143 ± 354.73 |
| $AUC_t$ (ng.h/mL) | 2920.615 ± 1073.07 | 2965.622 ± 702.79 |
| $AUC_\infty$ (ng.h/mL) | 3061.132 ± 1059.36 | 3090.534 ± 706.29 |
| $T_{max}$ (h)* | 1.15 ± 0.43 | 1.19 ± 0.48 |

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

| | **Amoxicillin (range)** | **Clavulanic Acid (range)** |
|---|---|---|
| $C_{max}$ | 0.992 (0.9006-1.0921) | 0.941 (8221-1.0779) |
| $AUC_t$ | 0.984 (8983 – 1.0773) | 0.944 (0.8369 – 1.0652) |
| $AUC_\infty$ | 0.988 (0.9013 – 1.0836) | 0.957 (0.8558 – 1.0693) |

There were no adverse events observed during the study.

The 90% confidence intervals for $AUC_{0\text{-}t}$, $C_{max}$ and $AUC_{0\text{-}inf}$ 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

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

## 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 457/5ml Suspension (PL 21880/0011) 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

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

## EFFICACY

Bioequivalence has been demonstrated between the applicant's Co-Amoxiclav 457/5ml Suspension and the reference product Augmentin 457mg/5ml Oral Suspension (Smithkline Beecham).

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the reference product.

## BENEFIT-RISK ASSESSMENT

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

# CO-AMOXICLAV 457MG/5ML SUSPENSION (PL 21880/0011)

## STEPS TAKEN FOR ASSESMENT

| | |
|---|---|
| 1 | The MHRA received the marketing authorisation applications on 4th January 2006 |
| 2 | Following standard checks and communication with the applicant the MHRA considered the applications valid on 13th February 2006 |
| 3 | Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 10th March 2006 and 30th June 2006, and further information relating to the quality dossiers on 17th May 2006, 17th March 2008 and 31st October 2008. |
| 4 | The applicant responded to the MHRA's requests, providing further information on 30th June 2006 and 1st February 2008 for the clinical sections, and again on 3rd March 2008, 22nd September 2008 and 30th December 2008 for the quality sections. |
| 5 | The applications were determined on 29th June 2009 |

# CO-AMOXICLAV 457MG/5ML SUSPENSION (PL 21880/0011)

## STEPS TAKEN AFTER AUTHORISATION - SUMMARY

| Date submitted | Application type | Scope | Outcome |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1 NAME OF THE MEDICINAL PRODUCT
Co-Amoxiclav 457mg/5ml Suspension

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION
After reconstitution, each 5ml of oral suspension contains 400 mg amoxicillin (as trihydrate) and 57 mg clavulanic acid (as potassium salt).

For full list of excipients, see section 6.1.

### 3 PHARMACEUTICAL FORM
Powder for oral suspension.
White powder.

### 4 CLINICAL PARTICULARS
#### 4.1 Therapeutic indications
Treatment of bacterial infections induced by gramnegative and grampositive amoxicillin-resistant microorganisms whose resistance is caused by β-lactamases which however are sensitive to the combination of amoxicillin and clavulanic acid.

Co-amoxiclav oral suspension is 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 (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
The usual recommended daily dosage is:
25/3.6 mg/kg/day in mild to moderate infections (upper respiratory tract infections, e.g. recurrent tonsillitis, lower respiratory infections and skin and soft tissue infections)
45/6.4 mg/kg/day for the treatment of more serious infections (upper respiratory tract infections, e.g. otitis media and sinusitis, lower respiratory tract infections, e.g. bronchopneumonia and urinary tract infections)

The tables below give guidance for children.

*Children over 2 years*

| | | |
|---|---|---|
| 25/3.6 mg/kg/day | 2 - 6 years (13 - 21 kg) | 2.5 ml Co-Amoxiclav 457 Suspension b.i.d. |
| | 7 - 12 years (22 - 40 kg) | 5.0 ml Co-Amoxiclav 457 Suspension b.i.d. |
| 45/6.4 mg/kg/day | 2 - 6 years (13 - 21 kg) | 5.0 ml Co-Amoxiclav 457 Suspension b.i.d. |
| | 7 - 12 years (22 - 40 kg) | 10.0 ml Co-Amoxiclav 457 Suspension b.i.d. |

*Children aged 2 months to 2 years*
Children under 2 years should be dosed according to body weight

| Weight (kg) | 25/3.6 mg/kg/day) | 45/6.4 mg/kg/day |
|---|---|---|
| | (ml/b.i.d.) | (ml/b.i.d.) |
| 2 | 0.3 | 0.6 |
| 3 | 0.5 | 0.8 |
| 4 | 0.6 | 1.1 |
| 5 | 0.8 | 1.4 |
| 6 | 0.9 | 1.7 |
| 7 | 1.1 | 2.0 |
| 8 | 1.3 | 2.3 |
| 9 | 1.4 | 2.5 |
| 10 | 1.6 | 2.8 |
| 11 | 1.7 | 3.1 |
| 12 | 1.9 | 3.4 |
| 13 | 2.0 | 3.7 |
| 14 | 2.2 | 3.9 |
| 15 | 2.3 | 4.2 |

There is insufficient experience with Co-Amoxiclav Oral Suspension to make dosage recommendations for children under 2 months old.

*Infants with immature kidney function*
For children with immature renal function Co-Amoxiclav Oral Suspension 457 is not recommended.

**Renal impairment**
For children with a GFR of >30 ml/min no adjustment in dosage is required. For children with a GFR of <30 ml/min Co-Amoxiclav Oral Suspension 457 is not recommended.

**Hepatic impairment**
Dose with caution; monitor hepatic function at regular intervals. There is, as yet, insufficient evidence on which to base a dosage recommendation.

**Method of administration**
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. Therapy can be started parenterally and continued with an oral preparation.

As a precaution, therapy over at least 10 days is indicated in the treatment of infections with β-haemolytic streptococci in order to guard against late complications (e.g. rheumatic fever, glomerulonephritis).

**4.3 Contraindications**
Hypersensitivity to amoxicillin, clavulanic acid, β-lactams (e.g. penicillins, cephalosporins) owing to the danger of anaphylactic shock, or to any of the excipients.

Co-amoxiclav oral suspension should not be used in patients in whom hepatic functional impairment has occurred during previous treatment with amoxicillin/clavulanic acid.

Amoxicillin/clavulanic acid must not be used in patients with severe hepatic functional impairment. Patients with infectious mononucleosis (glandular fever) and patients with lymphatic leukaemia have a higher risk of developing exanthema if given amoxicillin/clavulanic acid. Consequently amoxicillin/clavulanic acid should not be administered to patients with these conditions.

Phenylketonuria since the product contains aspartame.

**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 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 oral suspension 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 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.

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 oral suspension 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 concentrations 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 oral suspension may promote the occurrence of allergic cutaneous reactions (exanthema).

Amoxicllin/clavulanic acid and sufasalasin

Aminopenicillin may reduce the plasmatic concentration of sufasalasin.

Amoxicllin/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.

Amoxicllin/clavulanic acid and digoxin

An increase in absorption of digoxin is possible on concurrent administration with Co-amoxiclav oral suspension.

Amoxicillin/clavulanic acid and disulfiram
Co-amoxiclav oral suspension cannot be used concomitantly with disulfiram.

Amoxicllin/clavulanic acid and anticoagulants
A tendency to bleed can be potentiated due to concomitant administration of Co-amoxiclav oral suspension and anticoagulants of the cumarin class.

Amoxicllin/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.

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**

Data on approximately 560 exposed pregnancies indicate no adverse effects of amoxicillin/clavulanic acid on pregnancy or on the health of the foetus/newborn child. However 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. As a precautionary measure Co-amoxiclav oral suspension should only be used in pregnancy if in the judgement of the physician the potential benefits outweigh the possible hazards.

Both substances pass into the embryo/foetus by way of the placenta and are eliminated into breastmilk (nothing is known of the effects of clavulanic acid on the suckled infant). Consequently, diarrhoea and colonisation of the mucosae by yeasts are possible in the suckled infant so that in some cases it may be necessary to wean the infant. The possibility of sensitisation should be taken into account.

**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
Thrombocystosis, haemolytic anaemia

Very rare
Changes in blood count in form of leucopenia, agranulocytosis, granulocytopenia, 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, serume 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 patients 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**

a) Symptoms of intoxication
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, myocolonic jerks, coma, maemolytic reactions, renal failure and acidosis are possible. Shock can occur within 20 to 40 minutes in exceptional circumstances.

b) Management of intoxication
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**

**ATC Code: J01CA**

**Pharmacotherapeutic group: β-lactam antibacterials; combination of penicillin and beta-lactamase inhibitor**

Amoxicillin
Amoxicillin is a bactericidal semisynthetic aminobenzyl penicillin (p-hydroxy ampicillin). It inhibits cross-linking of structures of the cell wall by binding to transpeptidases. The resulting instability leads by way of lysis to death of the cell.

Clavulanic Acid
Clavulanic acid is a natural product of Streptomyces clavuligerus and its structure resembles that of the penicillin nucleus. It possesses only slight antibacterial activity itself but it irreversibly inhibits chromosome-coded beta-lactamases of Richmond classes II, IV and VI and plasmid-coded beta-lactamases of Richmond classes III and V.

By concomitant administration of clavulanic acid and amoxicillin the latter is protected from degradation by beta-lactamases. Consequently the combination of amoxicillin and clavulanic acid is active against numerous amoxicillin-resistant bacterial strains.

Breakpoints
The MIC breakpoints (NCCLS 2004) are expressed as the amoxicillin concentration. Bacteria are usually considered susceptible at <4μg/ml and resistant at >8 μg/ml, whilst M.catarrhalis β-lactamase negative are considered susceptible at <0.25 μg/ml and resistant at >0.5 μg/ml and H influenza β-lactamase negative are considered susceptible at <2 μg/ml. Str. pneumoniae are considered susceptible to A/C at MIC <2 μg/ml and resistant at >8 μg/ml.

Spectrum of action of amoxicillin/clavulanic acid:
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.

| **Commonly susceptible species** |
|---|
| Gram-positive<br>Enterococcus faecalis<br>Enterococcus faecium<br>Staphylococcus aureus (methicillin-susceptible)<br>Streptococcus pyogenes<br><br>Gram-negative<br>Haemophilus influenzae<br>Moraxella catarrhalis<br><br>Anaerobes<br>Bacteroides fragilis<br>Clostridium perfringens<br>Peptostreptococcus spp. |
| **Species for which acquired resistance may be a problem** |
| Gram-positive<br>Streptococcus pneumoniae+<br><br>Gram-negative<br>Escherichia coli<br>Klebsiella pneumoniae<br>Proteus mirabilis |
| **Resistant organisms** |
| Staphylococcus aureus (methicillin-resistant)<br>Pseudomonas aeruginosa<br>Legionella spp.<br>Chlamydia spp.<br>Mycoplasma spp. |

+ Rates of resistance vary within Europe

**Resistance**
Organisms that are normally resistant to amoxicillin 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 amoxicillin/clavulanate.

## 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.

Peak 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 ± 15% of a dose in unchanged form within 7 hours) and a small fraction is excreted in the bile. Total clearance ranges between approximately 250and 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 $LD_{50}$ 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**

Xanthan gum (E415)
Aspartame (E951)
Silicon dioxide (E551)
Colloidal silica
Anhydrous citric acid
Hypromellose
Flavour Orange Dry Powder
Flavour Raspberry Dry Powder
Flavour Golden Dry Powder

**6.2 Incompatibilities**

None known.

**6.3 Shelf life**

Dry powder: 2 years.
Reconstituted suspensions: 7 days when stored in a refrigerator (2-8°C).

**6.4 Special precautions for storage**

Powder for suspension: Do not store above 25°C. Keep the bottle tightly closed.
Reconstituted suspension: Store at 2-8°C. Do not freeze.

**6.5 Nature and contents of container**

107ml glass, round shaped bottle containing an off-white dry powder. The bottle is fitted with a polypropylene child resistant cap and packed in cartons with a 30ml measuring cup with 2.5ml graduations.

**6.6 Special precautions for disposal**

At time of dispensing, 58ml of water is added to the dry powder to form 70ml of oral suspension.

The Pharmacist should shake the suspension for 2 minutes and should then check for any particulates.

When reconstituted, an off-white suspension is formed

**7 MARKETING AUTHORISATION HOLDER**

Medreich PLC
9 Royal Parade,
Kew Gardens,
London,
TW9 3QD.

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 21880/0011

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

29/06/2009

**10 DATE OF REVISION OF THE TEXT**

29/06/2009

# PATIENT INFORMATION LEAFLET (PIL)

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

If your child gets any other problems while taking this medicine, tell your doctor or pharmacist.

## 5. HOW TO STORE CO-AMOXICLAV ORAL SUSPENSION

Keep out of the reach and sight of children.

- Do not use Co-amoxiclav Oral Suspension after the expiry date which is stated on the pack. The expiry date refers to the last day of that month.
- The suspension will be prepared by the pharmacist and is only suitable for use for up to 7 days after reconstitution. If any medicine is left after 7 days, return it to your pharmacist.
- Powder for suspension: Do not store above 25 °C. Keep the bottle tightly closed.
  Reconstituted suspension: Store at 2°- 8 °C. Do not freeze.

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

## 6. FURTHER INFORMATION

**What Co-Amoxiclav Oral Suspension contains**

- The active substances are amoxicillin (400mg) and clavulanic acid (57 mg) in every 5ml. Both of these ingredients are antibiotics and together they are known as co-amoxiclav.
- The other ingredients are: xanthan gum (E415), aspartame (E951), silicon dioxide (E551), colloidal silica, anhydrous citric acid, hypromellose, golden syrup, orange and raspberry flavours.

**What Co-Amoxiclav Oral Suspension looks like and the contents of the pack**

- When the powder has been reconstituted, Co-amoxiclav Oral suspension contains 400mg of amoxicillin (as trihydrate) and 57 mg clavulanic acid (as potassium salt), per 5 ml.
- Co-Amoxiclav Oral Suspension comes in a bottle containing 70 ml of an off-white liquid mixture called a suspension.

Pack size is a bottle containing 70 mls.

PL 21880/0011 POM

Date of leaflet preparation: June 2008

**Marketing Authorisation Holder and Manufacturer:**
The Marketing Authorisation Holder is:-
MEDREICH plc
9, Royal Parade, Kew Gardens,
Surrey TW9 3QD, England.



COXXXX 03.0000.08.00/E

# PACKAGE LEAFLET - INFORMATION FOR THE USER

**Co-Amoxiclav 457 mg/5ml Suspension**
Amoxicillin and Clavulanic Acid

**Read all of this leaflet carefully before giving your child this medicine**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask you doctor or pharmacist.
- This medicine has been prescribed for your child. Do not pass it on to others. It may harm them, even if their symptoms are the same as your child's.
- 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.

**In this leaflet**



## 1. WHAT CO-AMOXICLAV ORAL SUSPENSION IS AND WHAT IT IS USED FOR

Co-Amoxiclav Oral Suspension is an antibiotic for treating infections. It belongs to a group of antibiotics called 'penicillins'. Co-Amoxiclav Oral Suspension works by killing the bacteria that can cause infections. Co-Amoxiclav Oral Suspension 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 the urethra (the tube which carries urine from the bladder), kidneys and teeth and gums (abscesses).

## 2. BEFORE YOU GIVE CO-AMOXICLAV ORAL SUSPENSION TO YOUR CHILD

**Do not give to your child if:**

- You know that your child is allergic to penicillin (or any other antibiotic).
- Your child has ever had a skin rash or swelling of the face or neck when taking an antibiotic.
- Your child has ever had a serious complaint - such as liver problems - when taking an antibiotic.
- Your child has glandular fever.
- Your child has a blood disorder called lymphatic leukaemia
- Your child was born with a condition called 'phenylketonuria' as this product contains aspartame.

**Take special care with Co-Amoxiclav Oral Suspension**
**Tell your doctor before using this medicine if:**

- Your child is being treated for liver or kidney problems.
- Your child has severe diarrhoea.
- Your child has a catheter.
- Your child suffers from severe allergies or asthma.
- if there has already been long term use of this antibiotic as your doctor may decide to do blood tests to monitor your liver, kidneys or blood cells.

Your doctor may decide to give your child a different medicine or change the dose of Co-Amoxiclav Oral Suspension.

**Taking other medicines**
Please tell your doctor if you are taking any of the following medicines:
- Other antibiotics such as tetracyclines or sulphonamides
- Probenecid or allopurinol used to treat gout
- Sufasalasin
- Methotrexate used to treat rheumatoid arthritis
- Anticoagulants used to thin the blood including digoxin
- Disulfiram used to help in substance dependence such as nicotine and alcohol
- Contraceptive pill

**Pregnancy and breast- feeding**
IF YOU ARE AN ADULT TAKING Co-Amoxiclav Oral Suspension let your doctor know if you are pregnant (or if you think you could be). Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines**
Co-amoxiclav Oral suspension may cause confusion, dizziness or convulsions. IF YOU ARE AN ADULT TAKING Co-amoxiclav Oral Suspension make sure you are not affected before driving or using machinery.
**Important information about some of the ingredients of Co-amoxiclav Oral Suspension**
This product contains aspartame therefore if your child suffers from phenylketonuria contact your doctor before giving this medicine.

## 3. HOW TO GIVE CO-AMOXICLAV ORAL SUSPENSION

Always use Co-amoxiclav oral suspension exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. For children under two years the dose is based on the weight of your child.

The usual oral dose is given in the table below.

| Age of child | Usual dose |
|---|---|
| 2 months to 2 years | 25/3.6 mg/kg/day to 45/6.4 mg/kg/day as two daily doses |
| 2 to 6 years | 2.5 ml or 5 ml twice a day |
| 7 to 12 years | 5 ml or 10 ml twice a day |

Shake the bottle well before removing the cap. Slowly pour the medicine into the measuring cup provided.

Try to give your child Co-Amoxiclav Oral Suspension
- just before meals.
- evenly through the day.
- as part of the daily routine for example at the start of a meal, once in the morning and once in the evening.
- no more than one dose every 8 hours and never give two doses within about four hours of each other.

**Keep giving your child the medicine for the prescribed number of days, even if he or she seems to be better.**
Your child needs every dose to help fight off the infection. If you stop giving your child this medicine before the end of the prescribed time, some bacteria may survive and cause the infection to come back.
However you should not give your child this product for beyond two weeks without seeing your doctor again first.



**What if my child has been given more Co-Amoxiclav Oral Suspension than they should?**
If your child has been given too much Co-Amoxiclav Oral Suspension, contact your doctor or local hospital casualty department at once. Show the doctor the medicine bottle. Signs of overdose include nausea, sickness and diarrhoea, which may then be followed by sleepiness and fitting.

**What if I forget to give a dose of Co-Amoxiclav Oral Suspension?**
If you forget to give a dose don't worry - just give it as soon as youremember. But don't give your child the next dose too soon. Try to wait about four hours before giving the next dose. Always try to keep the doses evenly spaced. Do not give a double dose to make up for a forgotten dose.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, Co-Amoxiclav Oral Suspension can cause side effects, although not everybody gets them.
See your doctor straight away if:
- Your child gets severe diarrhoea with bleeding
- You notice your child's urine becoming darker or faeces (otherwise known as poo) becoming paler
- You notice your child's skin or the whites of your child's eyes turning yellow.

**Common** (between 1 in 10 and 1 in 100 patients)
- Diarrhoea, upset stomach, nausea (feeling sick) or vomiting (being sick).
  If this happens, the symptoms are usually mild and you may prevent them by giving your child each dose just before meals.
- Rash
  If your child starts to itch or gets a rash, stop giving Co-Amoxiclav Oral Suspension and tell your doctor at once.

**Uncommon** (between 1 in 100 and 1 in 1000 patients)
- Thrush (a yeast infection of the mouth, vagina or skin folds).

**Rare** (between 1 in 1000 and 1 in 10,000 patients)
- Slight yellow/brown staining of the teeth.
  Such staining usually disappears shortly after treatment if teeth are brushed regularly.
- Remind your doctor if your child is having blood tests asCo-Amoxiclav sometimes causes short term changes in blood cell counts. It can also cause an increase in bleeding time.
- Swollen face and breathing problems.

**Very rare** (less than 1 in 10,000 patients)
- Hyperactivity, dizziness headache, anxiety, sleeplessness, aggression or convulsions. These symptoms are reversible.
- This medicine may form crystals in the urine (usually only visible under a microscope) which may be characterised by cloudy urine or by difficulty/discomfort in passing urine.
- Black tongue.

Tell your doctor straightaway if your child has any of these symptoms. 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.

# LABELLING


Co-amoxiclav 457 mg/5 ml oral suspension
70 ml
70 ml
Co-amoxiclav 457 mg/5 ml oral suspension
contains penicillin
MEDREICH
To reconstitute add 58 ml water and shake until powder is completely dispersed.
Shake well before use.
For oral use.
Also contains aspartame (E951). See leaflet for further information.
When the powder has been reconstituted, Co-amoxiclav 457 mg oral suspension contains 400 mg amoxicillin (as trihydrate) and 57 mg clavulanic acid (as potassium salt), per 5 ml.
Affix dispensing label here
8 190104 256353
Co-amoxiclav 457 mg/5 ml oral suspension
70 ml
Co-amoxiclav 457 mg/5 ml oral suspension
contains penicillin
MEDREICH
70 ml
Co-amoxiclav 457 mg/5 ml oral suspension
contains penicillin
To be taken as directed by the physician.
Keep out of the reach and sight of children.
Powder for suspension: Do not store above 25°C. Keep the bottle tightly closed.
Reconstituted suspension: Store at 2-8°C. Do not freeze.
Shelf life after reconstitution: 7 days.
POM
PL No.: 21880/0011
SP - 46 / 76
MA Holder & Manufacturer:
MEDREICH plc
9, Royal Parade, Kew Gardens, Surrey TW9 3QD, England.
CXXXXX 02.XXXX.XX.XX
Co-amoxiclav 457 mg/5 ml oral suspension
70 ml
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