CO-AMOXICLAV 875/125MG DISPERSIBLE TABLETS LEK PL 16220/0001

CO-AMOXICLAV 500/125MG DISPERSIBLE TABLETS LEK PL 16220/0002

AMOKSIKLAV 875/125MG DISPERSIBLE TABLETS PL 16220/0003

AMOKSIKLAV 500/125MG DISPERSIBLE TABLETS PL 16220/0004

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LAY SUMMARY

The MHRA today granted Lek Pharmaceuticals dd Marketing Authorisations (licences) for the medicinal products Co-amoxiclav 875/125mg Dispersible Tablets Lek (PL 16220/0001), Co-amoxiclav 500/125mg Dispersible Tablets Lek (PL 16220/0002), Amoksiklav 875/125mg Dispersible Tablets (PL 16220/0003) and Amoksiklav 500/125mg Dispersible Tablets (PL 16220/0004). These are prescription-only medicines (POM) for the treatment of certain types of bacterial infection.

Co-amoxiclav and Amoksiklav Dispersible Tablets contain the active ingredients amoxicillin, which kills the bacteria that causing the infection, and clavulanic acid, which 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 and Amoksiklav Dispersible Tablets outweigh the risks, hence Marketing Authorisations have been granted.

CO-AMOXICLAV 875/125MG DISPERSIBLE TABLETS LEK PL 16220/0001

CO-AMOXICLAV 500/125MG DISPERSIBLE TABLETS LEK PL 16220/0002

AMOKSIKLAV 875/125MG DISPERSIBLE TABLETS PL 16220/0003

AMOKSIKLAV 500/125MG DISPERSIBLE TABLETS PL 16220/0004

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Co-amoxiclav 875/125mg Dispersible Tablets Lek (PL 16220/0001), Co-amoxiclav 500/125mg Dispersible Tablets Lek (PL 16220/0002), Amoksiklav 875/125mg Dispersible Tablets (PL 16220/0003) and Amoksiklav 500/125mg Dispersible Tablets (PL 16220/0004) to Lek Pharmaceuticals dd on 15th January 2007. The products are prescription-only medicines.

These are two sets of parallel applications for two strengths of amoxicillin and clavulanic acid dispersible tablets, submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming essential similarity to the original products Augmentin Tablets (Beecham Group Plc, UK).

The products contain the active ingredients amoxicillin and clavulanic acid. Amoxicillin is a β-lactam antibiotic, which possesses activity against some gram-positive and gram-negative aerobes and anaerobes. Its action, however, can be inhibited by β-lactamase producing bacteria strains. Clavulanic acid, which is a β-lactamase inhibitor, protects amoxicillin from inactivation by β-lactamase.

These applications for Co-amoxiclav 875/125mg Dispersible Tablets Lek, Co-amoxiclav 500/125mg Dispersible Tablets Lek, Amoksiklav 875/125mg Dispersible Tablets and Amoksiklav 500/125mg Dispersible Tablets were submitted at the same time and depend on the bioequivalence studies comparing the applicant's 625mg and 1,000mg dispersible tablets against Augmentin Tablets of the same strength. Consequently, sections of this Scientific Discussion refer to all products.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Both amoxicillin trihydrate and potassium clavulanate are controlled by monographs in the European Pharmacopoeia.

The drug substance manufacturers for both amoxicillin trihydrate and potassium clavulanate have provided relevant certificates of suitability to support the manufacture of the drug substance.

Appropriate specifications are provided for both active substances. These conform to the current monographs for each substance, with additional tests for residual solvents.

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

Potassium clavulanate is stored under nitrogen inside two LDPE bags, containing an antistatic agent and a dessicant, and stored in metal drums. Amoxicillin trihydrate is packed in a sealed polyethylene bag that is placed in a thermally-sealed aluminium bag, which is in turn placed in a cardboard drum.

Appropriate stability data have been generated supporting a retest period of 3 years for potassium clavulanate and 3-4 years for amoxicillin trihydrate (depending on the active ingredient manufacturer). These are all acceptable. Satisfactory commitments have been provided to continue stability testing on both active substances after marketing authorisations have been granted.

DRUG PRODUCT

The test products are fast disintegrating tablets which would be dispersible or orodispersible to allow user-friendly administration (to avoid swallowing large tablets the test Lek product can be dispersed in water or dispersed in the mouth prior to swallowing). The UK brand leader, Augmentin® is licensed as 375 mg, 625 mg and 1 g film-coated tablets and a 375 mg dispersible tablet. There is no dispersible form for the higher strengths.

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely tropical blend flavour, sweet orange flavour, aspartame, colloidal anhydrous silica, ferric oxide (E172), talc, castor oil (hydrogenated), and silicified microcrystalline cellulose. All excipients used comply with their respective Ph Eur monograph, with the exception of tropical blend flavour, orange flavour and silicified microcrystalline cellulose (which comply with an in-house specification) and ferric oxide (which complies with the French National Formulary). Satisfactory certificates of analysis have been provided for all excipients.

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

Dissolution and impurities

Dissolution of the dispersible tablets (test product) is faster than that of the reference product film-coated tablets, although after 30 minutes dissolution results are comparable. The impurity profiles were found to be similar to those of the reference product Augmentin Tablets.

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 each strength 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 in laminated (PVC/OPA) aluminium blisters. 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 24 months has been set, which is satisfactory. Storage conditions are “Do not store above 25 degrees C” and “Store in the original packaging”.

Bioequivalence
Satisfactory bioequivalence studies have been provided (see Clinical Assessment Section).

ADMINISTRATIVE
Expert Report
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics
These are consistent with those for the reference products and are satisfactory.

Labelling
These are satisfactory

Patient Information Leaflet
This is consistent with that for the reference products and is satisfactory.

MAA Forms
These are satisfactory.

Conclusion

It is recommended that Marketing Authorisations are granted for these applications.

The requirements for essential similarity of the proposed and reference products have been met with respect to qualitative and quantitative content of the active substance. In addition, similar dissolution profiles have been demonstrated for the proposed and reference products.

PRECLINICAL ASSESSMENT

These applications for generic products claims essential similarity to Augmentin Tablets (Beecham Group Plc, UK), which have been licensed within the EEA for over 10 years.

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

CLINICAL ASSESSMENT

TOXICOLOGY

No toxicological data is required for this submission.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Four comparative bioequivalence studies are presented in the submission dossier, two comparing the 1000mg Lek Quicktab versus the German comparator product 1000mg Augmentan Tablet and two comparing Amoksiklav 625mg Quicktab dispersible tablet versus the German comparator product GlaxoSmithKline Augmentan 625mg dispersible tablet.

The studies were conducted in Slovenia in 42 healthy fasting male volunteers.
Since 1000mg dispersible tablets are not licensed in the EU, the originator's film-coated tablet was chosen as the reference product.

The study protocols of all four studies state that they are conducted according to GMP.

BIOEQUIVALENCE

Study 0306 AMK2

This is a single-dose, randomised, 2-way crossover bioequivalence study of the Lek Co-Amoxiclav 1000mg Quicktab dispersible tablet and GlaxoSmithKline Augmentan 1000mg film-coated tablet.

The test formulation was given with 30 ml water, followed by 210 ml water; the reference tablet was taken whole with 240 ml water.

Blood samples were analysed by HPLC method and pharmacokinetic parameters were analysed using analysis of variance (ANOVA) suitable for a crossover design, in which sequences, subjects nested within sequences, treatments and periods were evaluated.

All subjects completed the study.

Results

Table 1: Summary pharmacokinetic variables [means(SD)]. From bioequivalence study Lek Co-Amoxiclav 1000mg dispersible tablet and GlaxoSmithKline Augmentan 1000mg film-coated tablet.

Amoxicillin

Parameter	Lek Co-Amoxiclav 1000 mg (Test)	GSK Augmentan 1000 mg (Ref)	Relative mean T:R (%)	90% CI
AUC_{0-t}(µg.hr/ml)*	3.50 (0.15)	3.37 (0.22)	114.20	108.20 – 120.53
AUC_{o-inf}(µg.hr/ml)*	3.52 (0.15)	3.38 (0.22)	113.95	108.0 – 120.23
C_{max} (µg./ml)*	2.52 (0.21)	2.30 (0.30)	124.89	115.50 – 135.04
t_{max} (hr)	1.35 (0.42)	1.65 (0.57)	-	-

*log transformed values

Clavulanic Acid

Parameter	Lek Co-Amoxiclav 1000 mg (Test)	GSK Augmentan 1000 mg (Ref)	Relative mean T:R (%)	90% CI
AUC_{0-t}(µg.hr/ml)*	1.65 (0.22)	1.61 (0.28)	103.60	97.43 – 110.16
AUC_{o-inf} (µg.hr/ml)*	1.69 (0.21)	1.65 (0.27)	103.46	97.51 – 109.77
C_{max} (µg./ml)*	0.96 (0.27)	0.91 (0.33)	105.32	97.49 – 113.78
t_{max} (hr)	1.07 (0.50)	1.21 (0.50)	-	-

*log transformed values

There were no adverse events during the study.

Study Conclusion
The results for the amoxicillin and clavulanic acid in this study met the criteria for bioequivalence.

Assessor's Comments
The relative mean pharmacokinetic parameters for amoxicllin and clavulanic acid are shown to be within the required parameters of 80-125% with the 90% confidence intervals also within these parameters with the exception of the confidence interval for amoxicillin (115-135%) but within wider based criteria of 70-143%. The differences in C_{max} is not unexpected in view of the difference in formulation between the test and reference product.

The bioequivalence of the AUC parameters indicates that the overall absorption of amoxicillin and clavulanic acid is equivalent from both products. The differences in C_{max} are not of clinical significance and would not be expected to influence the therapeutic efficacy and safety of co-amoxiclav. So the 1000mg test and reference product can be regarded as therapeutically equivalent.

Study 0321 AMK4
This also is a single-dose, randomised, 2-way crossover bioequivalence study of the Lek Co-Amoxiclav 1000mg Quicktab dispersible tablet and GlaxoSmithKline Augmentan 1000mg film-coated tablet.

Since 100mg dispersible tablets are not licensed in the EU, the originator's film-coated tablet was chosen as the reference product.

The test tablet was dispersed in 30 ml water in a glass and taken with the remaining 210 ml water, while the reference tablet was taken whole with 240 ml water.

Blood samples were analysed by HPLC method and pharmacokinetic parameters were analysed using analysis of variance (ANOVA) suitable for a crossover design, in which sequences, subjects nested within sequences, treatments and periods were evaluated.

Results
Table 2: Study AMK4 - Summary pharmacokinetic variables [means(SD)]. From bioequivalence study Lek Co-Amoxiclav 1000mg dispersible tablet and GlaxoSmithKline Augmentan 1000mg film-coated tablet.

Amoxicillin

Parameter	Lek Co-Amoxiclav 1000 mg ((Test)	GSK Augmentan 1000 mg (Ref)	Relative mean T:R (%)	90% CI
AUC_{0-t}(µg.hr/ml)*	3.53 ± 0.17	3.39 ± 0.27	114.83	108.12 – 121.96
AUC_{o-inf}(µg.hr/ml)*	3.55 ± 0.16	3.42 ± 0.26	114.82	1.08.25 – 121.78
C_{max} (µg./ml)*	2.57 ± 0.22	2.30 ± 0.31	130.58	121.96 – 139.80
t_{max} (hr)	1.22 ± 0.36	1.78 ± 0.76**	-	-

*log transformed values
**no statistically significant difference

Clavulanic Acid

Parameter	Lek Co-Amoxiclav 1000 mg (Test)	GSK Augmentan 1000 mg (Ref)	Relative mean T:R (%)	90% CI
AUC_{0-t}(µg.hr/ml)*	1.75 ± 0.20	1.66 ± 0.32	109.67	100.51 – 119.66
AUC_{o-inf}(µg.hr/ml)*	1.78 ± 0.20	1.70 ± 0.30	108.93	100.19 – 118.42
C_{max} (µg./ml)*	1.05 ± 0.23	0.92 ± 0.38	114.64	103.54 – 126.92
t_{max} (hr)	0.97 ± 0.38	1.27 ± 0.48	-	-

There were no adverse events during the study.

Study Conclusion

The results confirm those of the previous study AMK 0306 AMK2; the 1000mg Lek dispersible tablet is bioequivalent to the 1000mg Augmentan film-coated tablet as regards clavulanic acid and for AUC for amoxicillin. The results confirm the wider criteria for C_{max} (70-143%) for this parameter. A greater C_{max} for amoxicillin is not of therapeutic concern unless related to safety issues. In this study, the C_{max} did not exceed that for an 875/125mg coamoxiclav suspension.

Assessor's Comments

This study supports the results of the previous bioequivalence study 0306 AMK2 in showing that the test and reference products are bioequivalent for all pharmacokinetic parameters for clavulanic acid and for all but C_{max} for amoxicillin. The increased C_{max} for the dispersible Quicktabs is to be expected and of no clinical significance to the efficacy or safety of the co-amoxiclav dispersible tablet.

Study 0321 AMK1

This is a single-dose randomised, 2-way crossover bioequivalence study of the Amoksiklav 625mg Quicktab dispersible tablet and Glaxo SmithKline Augmentan 625mg dispersible tablet.

42 male healthy volunteers were recruited.

The test product was dispersed in the mouth, while the reference product was dissolved in 30 ml water in a glass.

Results

AMOXICILLIN		
Parameter	**Ratio Test/Ref.**	**90% confidence interval (%)**
InAUCT	101.83	99.75 – 103.96
InAUCI	101.87	99.82 – 103.96
InCMAX	95.81	91.29 – 100.55

CLAVULANIC ACID		
Parameter	**Ratio Test/Ref.**	**90% confidence interval (%)**
InAUCT	99.76	96.03 – 103.62
InAUCI	100.01	96.48 – 103.68
InCMAX	99.92	95.97 – 104.03

Study 0321 AMK6

This is a single-dose randomised, 2-way crossover bioequivalence study of the Amoksiklav 625mg Quicktab dispersible tablet and Glaxo SmithKline Augmentan 625mg film-coated dispersible tablet.

Both test and reference products were given orally, taken whole.

42 male healthy volunteers were recruited.

Results

AMOXICILLIN		
Parameter	**Ratio Test/Ref.**	**90% confidence interval (%)**
InAUCT	104.31	100.81 – 107.93
InAUCI	104.15	100.51 – 107.91
InCMAX	107.34	100.21 – 114.98

CLAVULANIC ACID		
Parameter	**Ratio Test/Ref.**	**90% confidence interval (%)**
InAUCT	105.98	97.78 – 114.87
InAUCI	105.84	98.40 – 113.85
InCMAX	107.83	100.76 – 115.41

The four bioequivalent studies, AMK2, AMK4, AMK1 and AMK6, outlined above have been reviewed in the Clinical Expert Report.

Assessor's Overall Comments on Bioequivalence

Both of the comparative bioequivalence studies for each of the two doses; 625mg and 1000mg Co-amoxiclav showed bioequivalence for both amoxicillin and clavulanic acid for AUC, but not for C_{max}. The higher C_{max} seen with the dispersible formulation is not unexpected and not clinically significant for the efficacy and safety of this antibiotic.

However, the test and reference products are different pharmaceutical forms; quickly dispersing and film-coated, respectively.

The additional factor of the crossover in the dispersion of the test and reference product in one of the studies for each dose, i.e. the dispersion in solution of the oral reference 625mg tablet in one study and the oral ingestion of the undispersed test product (AMK1) the test product in study AMK4, 1000mg, was taken orally without prior dispersion and the reference product was dispersed in solution shows that the AUC bioequivalence can be maintained in this crossover of dispersibility. Therefore, it is reasonable to conclude that

the difference in the dispersion rates between the test and reference products are not clinically significant and are therapeutically equivalent.

For the grant of the UK licences, only the bioequivalence studies comparing the 1000mg strengths were used as the German comparator product for these was identical pharmaceutically to the UK reference product and the criteria for showing dose linearity between the two strengths of test product was fulfilled. Based on these studies, bioequivalence was shown between the 875/125mg and 500/125mg strengths and their respective reference products.

Although the bioavailability studies for the 625mg strengths were not used, as the German comparator product is not similar to the UK reference product, the studies have been retained for the mutual recognition procedure as the data may be relevant for assessment by some member states.

6. EFFICACY

No efficacy data is required for this submission.

7. SAFETY

No safety data is required for this submission.

8. EXPERT REPORT

A Clinical Expert Report has been submitted and presents a Clinical Overview of coamoxiclav and reviews two of the bioavailability studies (AMK2 and AMK6) included in the submission dossier. A second document, which reviews the other two bioequvalence studies (AMK1 and AMK4), was later submitted with the accompanying study reports and data.

The clinical expert concludes that the 'Lek 1000mg Co-Amoxiclav dispersible/orodispersible tablets and Augmentin 1000mg film-coated tablets are bioequivalent in terms of AUC for amoxicillin and therapeutically equivalent in terms of C_{max} for amoxicillin. Since it does not contain any excipients known to have an influence on the safety and efficacy, the Lek product may be considered as a therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product.

9. SUMMARY OF PRODUCT CHARACTERISTICS

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

10. PATIENT INFORMATION LEAFLET

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

11. LABELLING

This is satisfactory.

12. MAA FORM

This is satisfactory.

13. DISCUSSION

The main evidence for this application is pharmacokinetic bioequivalence data. Two comparative bioavailability studies for each dose were submitted, both showing bioequivalence between the AUC's for amoxicillin and clavulanic acid. The higher C_{max} seen with the dispersible formulation is not unexpected and not clinically significant for the efficacy and safety of this antibiotic.

However, the test and reference products are different pharmaceutical forms; quickly dispersing and film-coated, respectively.

From the additional crossover in the dispersion of the test and reference product in one of the studies for each dose, i.e., the dispersion in solution of the oral reference 625mg tablet in one study and the oral ingestion of the undispersed test product (AMK1) the test product in study AMK4, 1000mg, was taken orally without prior dispersion and the reference product was dispersed in solution. This shows that the AUC bioequivalence can be maintained in this crossover of dispersibility and it is reasonable to conclude that the difference in the dispersion rates between the test and reference products are not clinically significant and are therapeutically equivalent.

For the grant of the UK licences, only the bioequivalence studies comparing the 1000mg strengths were used as the German comparator product for these was identical pharmaceutically to the UK reference product and the criteria for showing dose linearity between the two strengths of test product was fulfilled. Based on these studies, bioequivalence was shown between the 875/125mg and 500/125mg strengths and their respective reference products.

Although the bioavailability studies for the 625mg strengths were not used, as the German comparator product is not similar to the UK reference product, the studies have been retained in the applicant's dossier for future mutual recognition procedures, as the data may be relevant for assessment by some member states.

14. CONCLUSIONS

The grant of marketing authorisations is recommended.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Co-amoxiclav 875/125mg Dispersible Tablets Lek, Co-amoxiclav 500/125mg Dispersible Tablets Lek, Amoksiklav 875/125mg Dispersible Tablets and Amoksiklav 500/125mg Dispersible 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

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

EFFICACY

Bioequivalence has been demonstrated between the applicant's 875/125mg Dispersible Tablets and the German comparator product Augmantan 1000mg Film-Coated Tablets. As the German product used is pharmaceutically identical to the UK reference product Augmentin 1000mg Tablets, bioequivalence was shown between the applicant's 875/125mg Dispersible Tablets and the reference product. In addition, as linear kinetics apply between the 875/125mg and 500/125mg strength dispersible tablets, proportional formulae for the tablets have been used, and that similar dissolution results have been shown, bioequivalence has also been shown between the 500/125mg strength dispersible tablets and the reference product Augmentin 625mg Tablets.

No new or unexpected safety concerns arise from these applications.

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

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the 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 risk benefit is, therefore, considered to be positive.

CO-AMOXICLAV 875/125MG DISPERSIBLE TABLETS LEK PL 16220/0001

CO-AMOXICLAV 500/125MG DISPERSIBLE TABLETS LEK PL 16220/0002

AMOKSIKLAV 875/125MG DISPERSIBLE TABLETS PL 16220/0003

AMOKSIKLAV 500/125MG DISPERSIBLE TABLETS PL 16220/0004

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 29th March 2004
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 29th April 2004
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 29th September 2004, 22nd November 2004, 1st April 2005 and 22nd November 2006, and further information relating to the quality dossiers on 9th March 2005.
4	The applicant responded to the MHRA's requests, providing further information on 13th October 2004 and 27th November 2006 for the clinical sections, and again on 8th June 2005, 21st October 2005 for the quality sections.
5	The applications were determined on 15th January 2007

CO-AMOXICLAV 875/125MG DISPERSIBLE TABLETS LEK PL 16220/0001

CO-AMOXICLAV 500/125MG DISPERSIBLE TABLETS LEK PL 16220/0002

AMOKSIKLAV 875/125MG DISPERSIBLE TABLETS PL 16220/0003

AMOKSIKLAV 500/125MG DISPERSIBLE TABLETS PL 16220/0004

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-amoxiclav 875/125mg Dispersible Tablets Lek
Amoksiklav 875/125mg Dispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 875mg of amoxicillin in the form of amoxicillin trihydrate and 125mg clavulanic acid in the form of clavulanate potassium. For excipients, see 6.1

3 PHARMACEUTICAL FORM

dispersible / orodispersible tablet
Yellow brown mottled octagonal tablets with aromatic odour and taste of tropical fruit.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of the following bacterial infections when caused by amoxicillin-resistant but amoxicillin-clavulanate-susceptible microorganisms (see section 5.1):
Upper and lower respiratory tract infections, including:

- otitis media
- acute sinusitis
- acute exacerbation of chronic bronchitis
- community-acquired pneumonia
- Upper and lower urinary tract infections
- Skin and soft tissue infections
- Genito-urinary tract infections including septic abortion, pelvic or puerperal sepsis
- Intra-abdominal sepsis.

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

4.2 Posology and method of administration

Posology

Adults, adolescents (over 12 years of age and with a body weight of at least 40 kg).
The usual dose of amoxicillin/clavulanic acid is 250/62.5 mg to 500/125 mg three times daily, depending on age, body weight, renal function, severity and site of the infection, and expected or demonstrated pathogens.

Alternative tablet sizes are available; tablets should not be broken in order to achieve lower doses.

Therapy can be started parenterally and continued with an oral preparation.

Co-amoxiclav tablets 875/125 mg are not recommended in children of 12 years and under.

Dosage in renal impairment
The dose should be reduced in patients with renal functional impairment depending on the severity of the impairment and the patient's weight (see table).

Adults and adolescents
Dose in renal impairment in relation to patient weighing 70 kg:

GFR (ml/min)	Plasma creatinine	Single dose	Dose interval
> 30	< 2.5	No change in dosage	No change in dose interval
30-10	2.5 – 5.5	250/62.5 to 500/125 mg	12 h
< 10	>5.5	250/62.5 mg or 500/125 mg	12 h 24 h

Dosage in hemodialysis patients
Adults and adolescents: 250/62.5 mg per day and one dose during and after dialysis.

Each tablet contains 25 mg of potassium.

Children: not recommended.

Dosage in hepatic impairment:
Dose with caution; monitor hepatic function at regular intervals.

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

Co-amoxiclav must not be used in patients with severe hepatic functional impairment and in patients in whom hepatic functional impairment has occurred on previous therapy with Co-amoxiclav (see 4.3 and 4.4). Liver function parameters should be checked at regular intervals in patients with signs of hepatic lesions and a change of therapy should be given consideration if these parameters exacerbate on treatment.

Method of administration
Oral.

The tablets should be stirred in half a glass of water (minimum 30 ml), and mixed thoroughly before taking; or placed in the mouth to disperse, before being swallowed.
To minimise potential gastrointestinal intolerance, administer at a start of the meal.
Doses should be taken at regular intervals throughout the day, ideally at 12 hour intervals or as prescribed.

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

4.3 Contraindications
Co-amoxiclav is contraindicated in patients with a previous history of hypersensitivity to amoxicillin, clavulanic acid or any of the excipients.

Co-amoxiclav tablets must not be administered to patients with verified hypersensitivity to any beta-lactam drug (e.g. penicillins, cephalosporins, carbapenems, monobactams) owing to the danger of anaphylactic shock. Consequently, a careful history should be taken in regard to any allergic reactions before commencing treatment.

Co-amoxiclav tablets must not be used in patients with high-grade hepatic functional impairment and in patients in whom hepatic functional impairment has occurred during previous treatment with Co-amoxiclav, for example cholestatic jaundice induced by Co-amoxiclav or penicillin.

Patients with infectious mononucleosis (glandular fever) and patients with lymphatic leukemia have a higher risk of exanthema and consequently Co-amoxiclav tablets should not be administered during these diseases to treat concomitant bacterial infections.

4.4 Special warnings and precautions for use
Severe allergic reactions (including anaphylaxis) have been rarely reported following oral administration of amoxicillin/clavulanic acid (see section 4.8).

Although more likely in patients who have previously experienced beta-lactam hypersensitivity, these may occur in the absence of any such history. In such cases treatment with amoxicillin/clavulanic acid (see section 4.8).

In such cases treatment with amoxicillin/clavulanic acid 500/125 mg tablets should be discontinued immediately and appropriate management instituted.

Amoxicillin/clavulanic acid should be used with caution in patients with allergic diathesis, including asthma, since such patients may have a higher risk of allergic reactions to amoxicillin/clavulanic acid.

Patients with evidence of hepatic dysfunction should be treated with caution. Liver function parameters should be monitored in patients with signs or symptoms of hepatic impairment. Discontinuation of therapy should be considered in case of deterioration of liver function parameters during treatment.

In long term use (more than 10-14 days), regular monitoring of renal and hepatic function is recommended.

Patients suffering from severe gastrointestinal complaints including vomiting and diarrhoea should not be treated with oral amoxicillin/clavulanic acid since adequate absorption can not be guaranteed. In such cases, parenteral treatment is recommended.

Prolonged use of amoxicillin/clavulanic acid – or other broad spectrum antibiotics – may lead to superinfections due to an overgrowth of non-susceptible organisms and yeasts.

In case of severe and persistent diarrhoea, the possibility of pseudomembraneous colitis must be considered, in which case therapy should be discontinued.

In patients with renal impairment, excretion of amoxicillin and clavulanate will be delayed and, depending on the degree of the impairment, it may be necessary to reduce the total daily dosage (see section 4.2)

The presence of high urinary concentrations of amoxicillin can cause precipitation of the product in urinary catheters. Therefore, catheters should be visually inspected at intervals.
At high doses, adequate fluid intake and urinary output must be maintained to minimise the possibility of amoxicillin crystalluria.

4.5 Interaction with other medicinal products and other forms of interaction

Other antibacterial agents
There is a possibility that the antibacterial action of amoxicillin could be antagonised on co-administration with macrolides, tetracyclines, sulphonamides or chloramphenicol.

Probenecid
By inhibiting the renal elimination of amoxicillin (but not clavulanic acid) the concomitant administration of probenecid leads to an increase in the concentrations of amoxicillin in serum and bile.

Allopurinol
Concomitant administration of allopurinol may promote the occurrence of allergic cutaneous reactions.

Digoxin
An increase in the absorption of digoxin is possible on concurrent administration with amoxicillin.

Amoxicillin/clavulanic acid/disulfiram
Amoxicillin/clavulanic acid should not be used concurrently with disulfiram.

Methotrexate
Concomitant administration with methotrexate may lead to an increase in toxicity of methotrexate.

Anticoagulants
Concomitant administration of amoxicillin and coumarin anticoagulants, such as warfarin, may increase the incidence of bleeding.

Oral hormonal contraceptives
Administration of amoxicillin can transiently decrease the plasma level of oestrogens and progesterone, and may reduce the efficacy of oral contraceptives. Patients should be advised to use supplemental non-hormonal contraceptive measures.

Other forms of interaction
Amoxicillin may produce false positive results in glucose determination tests and tests for urobilinogen performed with nonenzymatic methods. Likewise the urobilinogen test can be affected.

Amoxicillin may decrease the amount of urinary estriol in pregnant women. Diarrhoea may decrease the absorption of other drugs and consequently have a negative influence on their effectivity.

Forced diuresis will lead to an increased elimination of amoxicillin resulting in decreased serum concentrations.

4.6 Pregnancy and lactation

Animal studies with orally and parenterally administered Co-amoxiclav have shown no teratogenic effects. There is limited experience of the use of Co-amoxiclav in human pregnancy.
Use of Co-amoxiclav tablets in pregnancy especially during the first trimester is not recommended unless considered essential by the physician.

Co-amoxiclav tablets can be administered to lactating mothers. Although trace quantities are excreted in breast milk there are no detrimental effects for the infant except for the risk of sensitisation.

4.7 Effects on ability to drive and use machines

Amoxicillin/clavulanic acid may sometimes be associated with side effects (such as rarely dizziness and even less often convulsions) that may impair the ability to drive a vehicle, to operate machinery and/or to work safely (see section 4.8).

4.8 Undesirable effects

The most commonly reported adverse drug reactions are hypersensitivity reactions:
Common (≥ 1% but < 10 %)
Cutaneous reactions such as exanthema, pruritus, urticaria; the typical morbilliform exanthema occurs 5 - 11 days after start of therapy. Immediate appearance of urticaria indicates an allergic reaction to amoxicillin and therapy should therefore be discontinued.

Rare (≥ 0.01% but < 0.1%): (see also section 4.4)
Angioneurotic oedema (Quincke's oedema)
Erythema multiforme exsudativum
Stevens-Johnson syndrome
Eosinophilia
Drug fever
Laryngeal oedema
Serum sickness
Haemolytic anaemia
Allergic vasculitis
Interstitial nephritis
Anaphylactic shock

Other possible side effects
Blood disorders:
There have been isolated reports of leucopenia, granulocytopenia, thrombocytopenia, pancytopenia, anaemia, myelosuppression, agranulocytosis, prolongation of bleeding time, and prolongation of prothrombin time. However, these changes were reversible on discontinuation of therapy.

Gastrointestinal disorders:
Common (≥ 1% but < 10%):
Gastric complaints, nausea, loss of appetite, vomiting, flatulence, soft stools, diarrhoea, enanthemas (particularly in the region of the mouth), dry mouth, taste disturbances. These effects on the

gastrointestinal system are mostly mild and frequently disappear either during the treatment or very soon after completion of therapy. The occurrence of these side-effects can generally be reduced by taking Co-amoxiclav during meals or with some food. If severe and persistent diarrhoea occurs, the very rare possibility of pseudomembranous colitis should be considered. The administration of anti-peristaltic drug is contraindicated.

Very rare (< 0.01%)
Development of black tongue.

Liver disorders:
Uncommon (≥ 0.1% but < 1%)
Moderate and transient increase of liver enzymes. Rare reports of hepatitis and cholestatic jaundice.

Renal disorders
Rare ≥ 0.01% but < 0.1%):
Acute interstitial nephritis may occur in rare cases.

CNS disorders
CNS effects have been seen rarely. They include hyperkinesia, dizziness and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Other undesirable effects
Prolonged and reported use of the preparation can result in superinfections and colonization with resistant organisms or yeasts such as oral and vaginal candidiasis.

4.9 Overdose

Symptoms of overdosage
In the event of overdosage, gastrointestinal symptoms, such as nausea, vomiting and diarrhoea, and disturbances of the fluid and electrolyte balance are possible. Also, convulsions may exist.

Management of overdosage
There is no specific antidote for overdose. Treatment consists of haemodialysis and symptomatic measures paying particular attention to the water and electrolyte balance, especially if there are gastro-intestinal symptoms. Administration of medicinal charcoal and gastric lavage are useful only in cases of very high overdose (>250 mg/kg). In case of severe renal insufficiency, Co-amoxiclav can be eliminated from the circulation via haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
Amoxicillin:
Amoxicillin is an acid-stable aminopenicillin that is susceptible to hydrolysis by common beta-lactamase enzymes.

Clavulanic acid:
Clavulanic acid is a beta-lactam molecule that is able to inhibit many of the most commonly occurring beta-lactamases such as staphylococcal penicillinases and enzymes of the TEM, OXA, SHV families (including many of the extended spectrum beta-lactamases of these groups). Thus, combination of amoxicillin with clavulanic acid maintains the activity of the aminopenicillin against organisms that produce sufficient quantities of these enzymes that would otherwise render inactive.

However, clavulanic acid is not able to inhibit the AmpC (Class I) beta-lactamases that may be produced by certain Gram-negative bacilli or the metallo-beta-lactamases (such as carbapenemases). Therefore, organisms that are normally susceptible to amoxicillin but have acquired the ability to produce any of these enzymes in amounts sufficient to render amoxicillin inactive would not be susceptible to Co-amoxiclav.

Antibacterial spectrum

MIC Breakpoints:

The MIC breakpoints according to the NCCLS criteria and methodology that separates susceptible (S) organisms from those that are intermediately susceptible (I) or resistant (R) are:

Enterobacteriaceae:	S ≤ 8/4mg/L;	I=16/8mg/L;	R≥32/16mg/L
Staphylococci:	S ≤ 4/2mg/L;		R ≥ 8/4mg/L
Haemophilus influenzae:	S ≤ 4/2mg/L;		R ≥ 8/4mg/L
Streptococcus pneumoniae:	S ≤ 0.5 / 0.25mg/L;	I=1/0.5mg/L;	R ≥ 2/1mg/L

BSAC criteria are as follows (Expressed as amoxicillin):

Enterobacteriaceae:	S ≤ 8 mg/L	R ≥ 16 mg/L
In UTI:	S ≤ 32 mg/L	R ≥ 64 mg/L

Haemophilus influenzae, *Moraxella catarrhalis*: S ≤ 1 mg/L R ≥2 mg/L.

Spectrum of action of Co-amoxiclav:

Micro-organisms	**Resistance - prevalence in EU***
SUSCEPTIBLE	
Gram-positive aerobes	
E. faecalis	
S. aureus methicillin-susceptible	
S. pneumoniae	0%-26%*
S. pyogenes	
Gram-negative organisms	
E. coli	5%-20%*
K. pneumoniae	7%*
H. influenzae	2%
M. cattarrhalis	
P. mirabilis *N. gonorrhoeae*	up to 34%
Anaerobes	
B. fragilis	
C. perfringens	
Peptostreptococcus spp.	
RESISTANT	
Gram-positive organisms	
E.faecium	
S.aureus methicillin-resistant	
Gram-negative organisms	
E.aerogenes	
E. cloacae	
M. morganii	
P. aeruginosa	
Serratia spp.	
P. rettgeri	
OTHERS	
Legionellae	
Chlamydia spp.	
Mycoplasma spp.	
Ricketsia spp.	

*It is recommended that local information on the epidemiology of resistant microorganisms should be consulted.

Resistance:

Microorganisms 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 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 250 and 370 mL/min. The serum half-life of amoxicillin in subjects with intact renal function is approximately 1 hour (0.9-1.2 h), in patients with creatinine clearance 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. Absorption is not affected by intake of food. 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
Investigations of the acute toxicity (LD_{50}) of amoxicillin and clavulanic acid in adult animals and neonates have confirmed very low toxicity potential. The LD_{50} of clavulanic acid (potassium salt) is determined by the potassium content. Administration of clavulanic acid (potassium salt) together with amoxicillin does not result in any unexpected or synergistic toxicity.

b) Chronic toxicity /subchronic toxicity
Not relevant.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tropical blend flavour
Sweet orange flavour
Aspartame E951
Colloidal anhydrous silica
Ferric oxide (yellow), E172
Talc
Castor oil, hydrogenated

Silicified microcrystaline cellulose (mixture of microcrystaline cellulose 98% and colloidal anhydrous silica 2%)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25°C.
Store in the original package.

6.5 Nature and contents of container
Alu/Alu blister foil in boxes of 10 (5x2) and 14 (7x2) tablets

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Lek Pharmaceuticals d.d. Verovškova 57, Ljubljana, Slovenia

8 MARKETING AUTHORISATION NUMBER(S)
16220/0001
16220/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
15/01/2007

10 DATE OF REVISION OF THE TEXT
15/01/2007

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-amoxiclav 500/125mg Dispersible Tablets Lek
Amoksiklav 500/125mg Dispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500mg of amoxicillin in the form of amoxicillin trihydrate and 125mg clavulanic acid in the form of clavulanate potassium.

For excipients, see 6.1

3 PHARMACEUTICAL FORM

dispersible / orodispersible tablet
Yellow brown mottled octagonal tablets with aromatic odour and taste of tropical fruit.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of the following bacterial infections when caused by amoxicillin-resistant but amoxicillin-clavulanate-susceptible microorganisms (see section 5.1):
Upper and lower respiratory tract infections, including:

- otitis media
- acute sinusitis
- acute exacerbation of chronic bronchitis
- community-acquired pneumonia
- Upper and lower urinary tract infections
- Skin and soft tissue infections
- Genito-urinary tract infections including septic abortion, pelvic or puerperal sepsis
- Intra-abdominal sepsis.

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

4.2 Posology and method of administration

Posology

Adults, adolescents (over 12 years of age and with a body weight of at least 40 kg)
The usual dose of amoxicillin/clavulanic acid is 250/62.5 mg to 500/125 mg three times daily, depending on age, body weight, renal function, severity and site of the infection, and expected or demonstrated pathogens.

Alternative tablet sizes are available; tablets should not be broken in order to achieve lower doses.

Therapy can be started parenterally and continued with an oral preparation.

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

Dosage in renal impairment
The dose should be reduced in patients with renal functional impairment depending on the severity of the impairment and the patient's weight (see table).

Adults and adolescents
Dose in renal impairment in relation to a patient weighing 70 kg:

GFR (ml/min)	Plasma creatinine	Single dose	Dose interval
> 30	< 2.5	No change in dosage	No change in dose interval
30-10	2.5 – 5.5	250/62.5 to 500/125 mg	12 h
< 10	>5.5	250/62.5 mg or 500/125 mg	12 h 24 h

Dosage in haemodialysis patients
Adults and adolescents: 250/62.5 mg per day and one dose during and after dialysis. Each tablet contains 25 mg potassium.

Children: not recommended

Dosage in hepatic impairment
Dose with caution; monitor hepatic function at regular intervals.

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

Co-amoxiclav must not be used in patients with severe hepatic functional impairment and in patients in whom hepatic functional impairment has occurred on previous therapy with Co-amoxiclav (see 4.3 and 4.4). Liver function parameters should be checked at regular intervals in patients with signs of hepatic lesions and a change of therapy should be given consideration if these parameters exacerbate on treatment.

Method of Administration
Oral: The tablets should be stirred in half a glass of water (minimum 30 ml), and mixed thoroughly before taking or placed in the mouth to disperse, before being swallowed.
To minimise potential gastrointestinal intolerance administer at a start of a meal.

Doses should be taken at regular intervals throughout the day, ideally at 8 hour intervals or as prescribed.

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

4.3 Contraindications
Co-amoxiclav is contraindicated in patients with a previous history of hypersensitivity to amoxicillin, clavulanic acid or any of the excipients.

Co-amoxiclav tablets must not be administered to patients with verified hypersensitivity to any beta-lactam drug (eg; penicillins, cephalosporins, carbapenems, monobactams) owing to the danger of anaphylactic shock. Consequently, a careful history should be taken in regard to any allergic reactions before commencing treatment.

Co-amoxiclav tablets must not be used in patients with high-grade hepatic functional impairment and in patients in whom hepatic functional impairment has occurred during previous treatment with Co-amoxiclav, for example cholestatic jaundice induced by Co-amoxiclav or penicillin.

Patients with infectious mononucleosis (glandular fever) and patients with lymphatic leukemia have a higher risk of exanthema and consequently Co-amoxiclav tablets should not be administered during these diseases to treat concomitant bacterial infections.

4.4 Special warnings and precautions for use
Severe allergic reactions (including anaphylaxis) have been rarely reported following oral administration of amoxicillin/clavulanic acid (see section 4.8).

Although more likely in patients who have previously experienced beta-lactam hypersensitivity, these may occur in the absence of any such history. In such cases treatment with amoxicillin/clavulanic acid 500/125 mg tablets should be discontinued immediately and appropriate management instituted.

Amoxicillin/clavulanic acid should be used with caution in patients with allergic diathesis, including asthma, since such patients may have a higher risk of allergic reactions to amoxicillin/clavulanic acid.

Patients with evidence of hepatic dysfunction should be treated with caution. Liver function parameters should be monitored in patients with signs or symptoms of hepatic impairment. Discontinuation of therapy should be considered in case of deterioration of liver function parameters during treatment.

In long-term use (more than 10-14 days), regular monitoring of renal and hepatic function is recommended.

Patients suffering from severe gastrointestinal complaints including vomiting and diarrhoea should not be treated with oral amoxicillin/clavulanic acid since adequate absorption can not be guaranteed. In such cases, parenteral treatment is recommended.

Prolonged use of amoxicillin/clavulanic acid – or other broad spectrum antibiotics – may lead to superinfections due to an overgrowth of non-susceptible organisms and yeasts.

In case of severe and persistent diarrhoea, the possibility of pseudomembraneous colitis must be considered, in which case therapy should be discontinued.

In patients with renal impairment, excretion of amoxicillin and clavulanate will be delayed and, depending on the degree of the impairment, it may be necessary to reduce the total daily dosage (see section 4.2).

The presence of high urinary concentrations of amoxicillin can cause precipitation of the medicinal product in urinary catheters. Therefore, catheters should be visually inspected at intervals.

At high doses, adequate fluid intake and urinary output must be maintained to minimise the possibility of amoxicillin crystalluria.

4.5 Interaction with other medicinal products and other forms of interaction

Other antibacterial agents:
There is a possibility that the antibacterial action of amoxicillin could be antagonised on co-administration with macrolides, tetracyclines, sulphonamides or chloramphenicol.

Probenecid
By inhibiting the renal elimination of amoxicillin (but not clavulanic acid) the concomitant administration of probenecid leads to an increase in the concentrations of amoxicillin in serum and bile.

Allopurinol
Concomitant administration of allopurinol may promote the occurrence of allergic cutaneous reactions.

Digoxin
An increase in the absorption of digoxin is possible on concurrent administration with amoxicillin.

Amoxicillin/clavulanic acid/disulfiram
Amoxicillin/clavulanic acid should not be used concurrently with disulfiram.

Methotrexate
Concomitant administration with methotrexate may lead to an increase in toxicity of methotrexate.

Anticoagulants
Concomitant administration of amoxicillin and coumarin anticoagulants, such as warfarin, may increase the incidence of bleeding.

Oral hormonal contraceptives
Administration of amoxicillin can transiently decrease the plasma level of oestrogens and progesterone, and may reduce the efficacy of oral contraceptives. Patients should be advised to use supplemental non-hormonal contraceptive measures.

Other forms of interaction
Amoxicillin may produce false positive results in glucose determination tests and tests for urobilinogen performed with nonenzymatic methods. Likewise the urobilinogen test can be affected.

Amoxicillin may decrease the amount of urinary estriol in pregnant women. Diarrhoea may decrease the absorption of other drugs and consequently have a negative influence on their effectivity.

Forced diuresis will lead to an increased elimination of amoxicillin resulting in decreased serum concentrations.

4.6 Pregnancy and lactation

Animal studies with orally and parenterally administered Co-amoxiclav have shown no teratogenic effects. There is limited experience of the use of Co-amoxiclav in human pregnancy.

Use of Co-amoxiclav tablets in pregnancy especially during the first trimester is not recommended unless considered essential by the physician.

Co-amoxiclav tablets can be administered to lactating mothers. Although trace quantities are excreted in breast milk there are no detrimental effects for the infant except for the risk of sensitisation.

4.7 Effects on ability to drive and use machines

Amoxicillin/clavulanic acid may sometimes be associated with side effects (such as rarely dizziness and even less often convulsions) that may impair the ability to drive a vehicle, to operate machinery and/or to work safely (see section 4.8).

4.8 Undesirable effects

The most commonly reported adverse drug reactions are hypersensitivity reactions:
Common (≥ 1% but < 10%)
Cutaneous reactions such as exanthema, pruritus, urticaria; the typical morbilliform exanthema occurs 5 - 11 days after start of therapy. Immediate appearance of urticaria indicates an allergic reaction to amoxicillin and therapy should therefore be discontinued.

Rare (≥ 0.01% but < 0.1%): (see also section 4.4)
Angioneurotic oedema (Quincke's oedema)
Erythema multiforme exsudativum
Stevens-Johnson syndrome
Eosinophilia
Drug fever
Laryngeal oedema
Serum sickness
Haemolytic anaemia
Allergic vasculitis
Interstitial nephritis
Anaphylactic shock

Other possible side effects
Blood disorders:
There have been isolated reports of leucopenia, granulocytopenia, thrombocytopenia, pancytopenia, anaemia, myelosuppression, agranulocytosis, prolongation of bleeding time, and prolongation of prothrombin time. However, these changes were reversible on discontinuation of therapy.

Gastrointestinal disorders:
Common (≥ 1% but < 10%):
Gastric complaints, nausea, loss of appetite, vomiting, flatulence, soft stools, diarrhoea, enanthemas (particularly in the region of the mouth), dry mouth, taste disturbances. These effects on the gastrointestinal system are mostly mild and frequently disappear either during the treatment or very soon after completion of therapy. The occurrence of these side-effects can generally be reduced by taking the medicinal product during meals or with some food. If severe and persistent diarrhoea

occurs, the very rare possibility of pseudomembranous colitis should be considered. The administration of anti-peristaltic drug is contraindicated.

Very rare (< 0.01%)
Development of black tongue.

Liver disorders:
Uncommon (≥ 0.1% but < 1%)
Moderate and transient increase of liver enzymes. Rare reports of hepatitis and cholestatic jaundice.

Renal disorders
Rare (≥ 0.01% but < 0.1%):
Acute interstitial nephritis may occur in rare cases.

CNS disorders
CNS effects have been seen rarely. They include hyperkinesia, dizziness and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Other undesirable effects
Prolonged and reported use of the medicinal product can result in superinfections and colonization with resistant organisms or yeasts such as oral and vaginal candidiasis.

4.9 Overdose

Symptoms of overdosage
In the event of overdosage, gastrointestinal symptoms, such as nausea, vomiting and diarrhoea, and disturbances of the fluid and electrolyte balance are possible. Also, convulsions may exist.

Management of overdosage
There is no specific antidote for overdose. Treatment consists of haemodialysis and symptomatic measures paying particular attention to the water and electrolyte balance, especially if there are gastro-intestinal symptoms. Administration of medicinal charcoal and gastric lavage are useful only in cases of very high overdose (>250 mg/kg). In case of severe renal insufficiency, Co-amoxiclav can be eliminated from the circulation via haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

Clavulanic acid:
Clavulanic acid is a beta-lactam molecule that is able to inhibit many of the most commonly occurring beta-lactamases such as staphylococcal penicillinases and enzymes of the TEM, OXA, SHV families (including many of the extended spectrum beta-lactamases of these groups). Thus, combination of amoxicillin with clavulanic acid maintains the activity of the aminopenicillin against organisms that produce sufficient quantities of these enzymes that would otherwise render inactive.

However, clavulanic acid is not able to inhibit the AmpC (Class I) beta-lactamases that may be produced by certain Gram-negative bacilli or the metallo-beta-lactamases (such as carbapenemases). Therefore, organisms that are normally susceptible to amoxicillin but have acquired the ability to produce any of these enzymes in amounts sufficient to render amoxicillin inactive would not be susceptible to Co-amoxiclav.

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

Spectrum of action of Co-amoxiclav:

Micro-organisms	Resistance - prevalence in EU*
SUSCEPTIBLE	
Gram-positive aerobes	
E. faecalis	
S. aureus methicillin-susceptible	
S. pneumoniae	0%-26%*
S. pyogenes	
Gram-negative organisms	
E. coli	5%-20%*
K. pneumoniae	7%*
H. influenzae	2%
M. catarrhalis	
P. mirabilis *N. gonorrhoeae*	up to 34%
Anaerobes	
B. fragilis	
C. perfringens	
Peptostreptococcus spp.	
RESISTANT	
Gram-positive organisms	
E.faecium	
S.aureus methicillin-resistant	
Gram-negative organisms	
E.aerogenes	
E. cloacae	
M. morganii	
P. aeruginosa	
Serratia spp.	
P. rettgeri	
OTHERS	
Legionellae	
Chlamydia spp.	
Mycoplasma spp.	
Ricketsia spp.	

*It is recommended that local information on the epidemiology of resistant microorganisms should be consulted.

Resistance:
Microorganisms 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 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 250 and 370 mL/min. The serum half-life of amoxicillin in subjects with intact renal function is approximately 1 hour (0.9–1.2 h), in patients with creatinine clearance 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. Absorption is not affected by intake of food. 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
Investigations of the acute toxicity (LD_{50}) of amoxicillin and clavulanic acid in adult animals and neonates have confirmed very low toxicity potential. The LD_{50} of clavulanic acid (potassium salt) is determined by the potassium content. Administration of clavulanic acid (potassium salt) together with amoxicillin does not result in any unexpected or synergistic toxicity.

b) Chronic toxicity /subchronic toxicity
Not relevant.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tropical blend flavour
Sweet orange flavour
Aspartame E951
Colloidal anhydrous silica
Ferric oxide (yellow), E172
Talc
Castor oil, hydrogenated

Silicified microcrystaline cellulose (mixture of microcrystaline cellulose 98% and colloidal anhydrous silica 2%)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25°C.
Store in the original package.

6.5 Nature and contents of container
Alu/Alu blister foil in boxes of 10 (5x2) and 14 (7x2) tablets

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Lek Pharmaceuticals d.d. Verovškova 57, Ljubljana, Slovenia

8 MARKETING AUTHORISATION NUMBER(S)
16220/0002
16220/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
15/01/2007

10 DATE OF REVISION OF THE TEXT
15/01/2007

PATIENT INFORMATION LEAFLET (PIL)

Please read all of this leaflet carefully before you start taking this medicinal product.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicinal product has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

Co-amoxiclav 875/125 mg Dispersible Tablets Lek

The active substances are amoxicillin and clavulanic acid

Marketing authorisation holder: Lek Pharmaceuticals d.d. Verovškova 57, Ljubljana, Slovenia

Manufacturer: Lek Pharmaceuticals d.d. Verovškova 57, Ljubljana, Slovenia

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

Each tablet contains 875mg of amoxicillin in the form of amoxicillin trihydrate and 125mg clavulanic acid in the form of clavulanate potassium. Each tablet also contains 25mg of potassium.
The other ingredients are tropical blend flavour, sweet orange flavour, aspartame E951, colloidal anhydrous silica, ferric oxide (yellow) E172, talc, castor oil hydrogenated, silicified microcrystalline cellulose
Your tablets are yellow brown mottled octagonal tablets with aromatic odour and taste of tropical fruit.
Your tablets come in blister packs of 10 (5x2) and 14 (7x2) tablets
Co-amoxiclav is a broad spectrum antibiotic for treating infections. It belongs to a group of antibiotics called »penicillins«. It is a combination of two active ingredients amoxicillin and clavulanic acid. Amoxicillin works by killing the bacteria that can cause the infections and clavulanic acid protects amoxicillin from bacterial degradation.

Why has your doctor prescribed Co-amoxiclav?
Co-amoxiclav can treat a wide range of bacterial infections including those of the chest (bronchitis, pneumonia), sinuses (sinusitis), ears (otitis media), skin and soft tissue (including animal bites), the bladder or urethra (the tube which carries urine from the bladder), kidneys and abdomen.

2. BEFORE YOU TAKE CO-AMOXICLAV

Let your doctor know if any of the following apply to you:
- You know you are allergic to penicillins (or any other antibiotic) or any of the ingredients of the medicinal product.
- You have asthma, since there is a higher risk of allergic reactions to amoxicillin and clavulanic acid.
- You have ever had a skin rash or swelling of the face or neck or difficulty with breathing when taking a medicinal product.
- You have ever had a serious complaint - such as liver problems (cholestatic jaundice or liver dysfunction) - when taking an antibiotic.
- You are or think you might be pregnant.
- You are breast-feeding.
- You suffer from kidney or liver problems (you are being treated for kidney or liver problems).
- You have glandular fever (infectious mononucleosis) or lymphatic leukaemia.
- You are under 12 years of age (or patient is under 12 years of age).
- If you are suffering from diarrhoea or vomiting, this may reduce the efficacy of your medicine.
- If you are having blood and urine tests for a substance in bile called urobilinogen because false positive results may occur.

Breast-feeding
Small amounts of amoxicillin may enter the breast milk and can occasionally cause diarrhoea or mouth infections in infants. Infants may also become allergic to amoxicillin. If you are breast feeding, discuss this with your doctor before taking Co-amoxiclav.

Important information about some of the ingredients of Co-amoxiclav
Your tablets contain potassium, which may be harmful for patients on low potassium diet (hyperkalemia). The tablets also contain aspartame, a source of phenyalanine which may be harmful for people with phenylketonuria, and castor oil hydrogenated which may cause stomach upset and diarrhoea.

Taking other medicines
Please inform your doctor if you are taking any other medicinal product – even those not prescribed because concomitant administration of medicinal product may influence efficacy.
- You are taking any medicinal product (such as warfarin) to prevent blood clots (anticoagulants). The activity of anticoagulants may increase.
- You are taking probenecid because this can cause the blood concentrations of amoxicillin to increase.
- You are taking digoxin (a heart medicine) because blood concentrations of this drug may increase.
- You are taking allopurinol (treatment of gout) concomitant use increases the incidence of skin reactions.
- Metotrexate (concomitant use of Co-amoxiclav may increase metotrexate's toxicity).
- You are taking disulfiram, since it should not be used concurrently with Co-amoxiclav.
- You are taking a contraceptive pill (Co-amoxiclav may decrease the reliability of the contraceptive effect, in this case you will need to take extra measures to prevent pregnancy, for example use of condom).
- You are taking certain other antibiotics called macrolides, tetracycline, chloramphenicol, or sulphonamides because the effect of amoxicillin may be reduced.

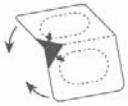
If any of the above do apply to you, your doctor may decide you need a different medicinal product instead of Co-amoxiclav or a different dose of Co-amoxiclav.

Effects on laboratory tests:
Laboratory tests (urinary sugar) may show wrong results.

3. HOW TO TAKE CO-AMOXICLAV

These tablets are usually prescribed for adults and children over 12 years and with the body weight of at least 40 kg:
The usual dose is one tablet two times a day (every 12 hours).
Your doctor will prescribe you the exact dosage; do not change it by yourself.
Never take more than recommended dose each day.

The tablets are available in blisters with 2 tablets. Break the blister card at perforation. Lift the coloured triangle and draw in the arrow direction. Do not push the tablet through the foil.



Drawing 1

Drawing 2

Drawing 3

Disperse the tablet either in half a glass of water (mix thoroughly) or in the mouth before swallowing.
To minimize potential gastrointestinal intolerance take the tablets just before meals.

Finish the full course prescribed by your doctor even if you feel better. If you stop treatment too early worsening or reappearance of infection is possible.

If you still feel unwell after finishing the treatment, go and see your doctor again first.
You should not use this medicinal product beyond two weeks without seeing your doctor again.

What if you forget to take a tablet?
If you forget to take a tablet, take it as soon as you remember. Then carry on as before. Try to wait about four hours before taking the next dose. Do not take two doses within an hour or so.

What if you take more tablets than you should?
If you have taken too many tablets all at once, contact your doctor or local hospital casualty department at once. Show the doctor your pack of tablets.

4. POSSIBLE SIDE EFFECTS

Like all other medicinal products, Co-amoxiclav may sometimes cause side effects, which are generally mild and transient.
Common side effects occur in less than 1 in 10 patients but more than 1 in 100.
Uncommon side effects occur in less than 1 in 100 patients but more than 1 in a 1000.
Rare side effects occur in less than 1 in 1000 patients but more than 1 in 10,000 patients.
Very rare side effects occur in less than 1 in 10,000 patients.

Allergic reactions may occur commonly during Co-amoxiclav treatment but severe allergic reactions are rare but if any of the following happens, stop taking Co-amoxiclav and tell your doctor immediately. You might need urgent medical attention or hospitalisation.

Skin rashes, itching; some sort of rash may occur commonly. Blistering or peeling of the skin, with or without ulceration in the mouth and sore eyes and genitals are rare side effects.
In rare cases there may be joint pain and fever, breathing problems, sweating, rapid heart beat or loss of consciousness.

Other rare side effects that may be due to allergy are increases in numbers of one type of white blood cells called eosinophils, drops in numbers of red blood cells, causing anemia, inflammation and damage to the blood vessels causing purple spots or blotches in and under the skin, and inflammation of the kidney.

Also tell your doctor immediately:
- if your skin or the whites of your eyes turn yellow, your urine turns dark or faeces become very pale.
- If you get severe diarrhoea with or without bleeding;
- If you have severe diarrhoea, with or without bleeding
- If you have a fit.
- If you have abnormal bruising or notice that you bleed for longer after minor wounds.
- If you have pain in the area of the kidneys (this will feel like low back pain).

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

If you get any other problems while taking this medicinal product, please tell your doctor or pharmacist.

5. STORING CO-AMOXICLAV

Do not store above 25°C.
Store in the original package.
Keep out of reach and sight of children.
Do not take your tablets after the expiry date printed on the package.
You should take any unused tablets or tablets that are out of date back to your pharmacist.
These tablets are only for you. Only a doctor can prescribe them for you. Never give them to anyone else.

This leaflet was written: November 2006

lek

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The active substances are amoxicillin and clavulanic acid

Marketing authorisation holder: Lek Pharmaceuticals d.d. Verovškova 57, Ljubljana, Slovenia

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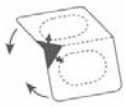

Drawing 1

Drawing 2

Drawing 3

Disperse the tablet either in half a glass of water (mix thoroughly) or in the mouth before swallowing.
To minimize potential gastrointestinal intolerance take the tablets just before meals.

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These tablets are only for you. Only a doctor can prescribe them for you. Never give them to anyone else.

This leaflet was written: November 2006

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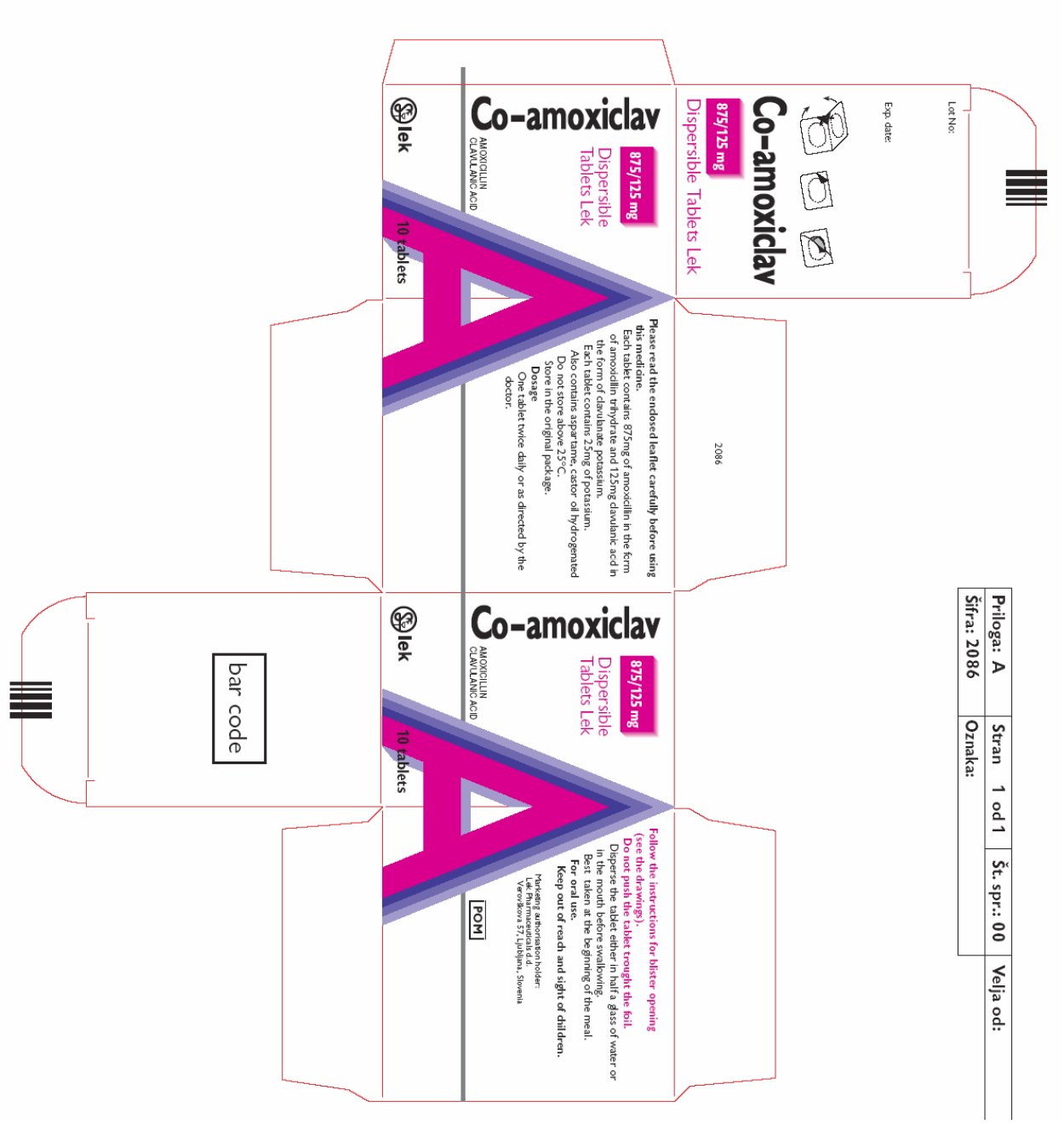
LABELLING


Lot No:
Exp. date:
Co-amoxiclav
875/125 mg
Dispersible Tablets Lek
2086
Please read the enclosed leaflet carefully before using this medicine.
Each tablet contains 875mg of amoxicillin in the form of amoxicillin trihydrate and 125mg clavulanic acid in the form of clavulanate potassium.
Each tablet contains 25mg of potassium.
Also contains aspartame, castor oil hydrogenated
Do not store above 25°C.
Store in the original package.
Dosage
One tablet twice daily or as directed by the doctor.
lek
Co-amoxiclav
875/125 mg
Dispersible Tablets Lek
AMOXICILLIN
CLAVULANIC ACID
10 tablets
bar code
Follow the instructions for blister opening (see the drawings).
Do not push the tablet trought the foil.
Disperse the tablet either in half a glass of water or in the mouth before swallowing.
Best taken at the beginning of the meal.
For oral use.
Keep out of reach and sight of children.
Marketing authorisation holder:
Lek Pharmaceuticals d.d.
Verovškova 57, Ljubljana, Slovenia
POM
Priloga: A
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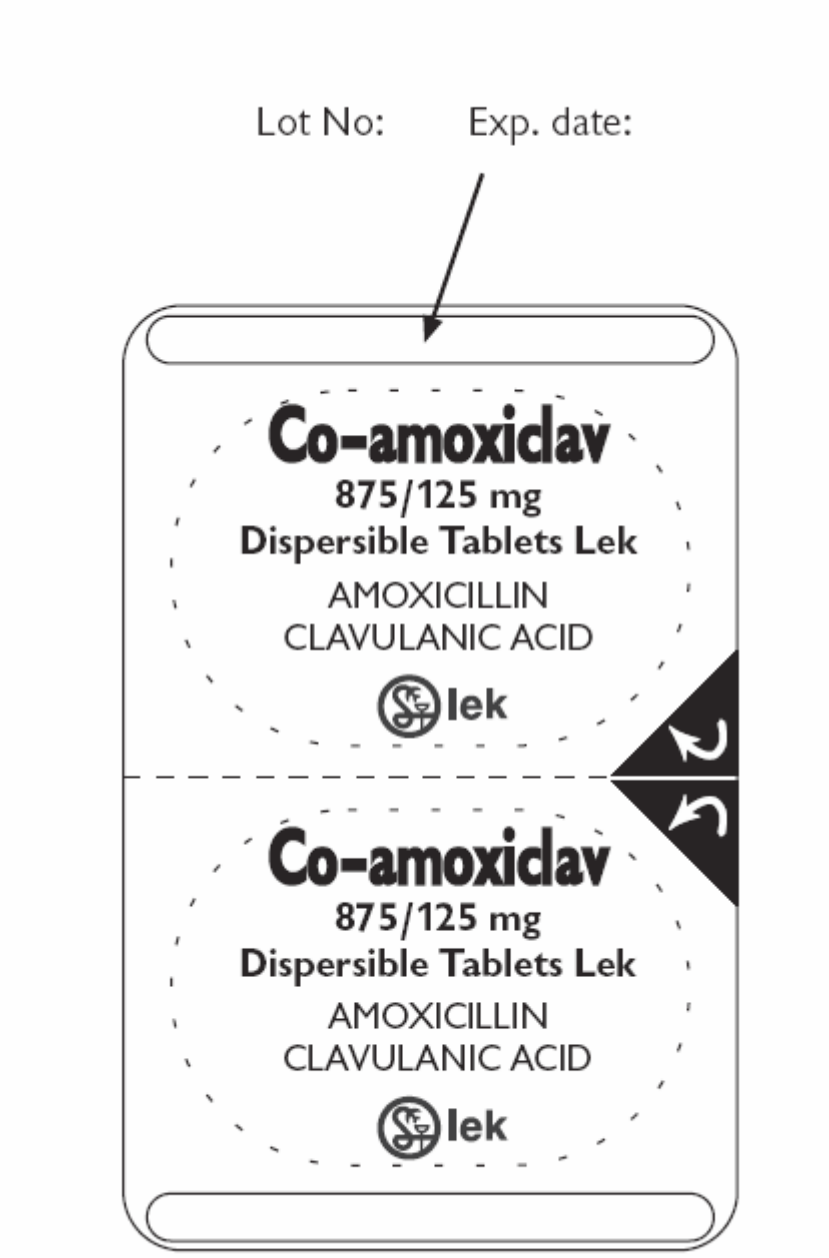
Velja od:
Šifra: 2086
Oznaka:


Lot No:
Exp. date:
Co-amoxiclav
875/125 mg
Dispersible Tablets Lek
AMOXICILLIN
CLAVULANIC ACID
lek
Co-amoxiclav
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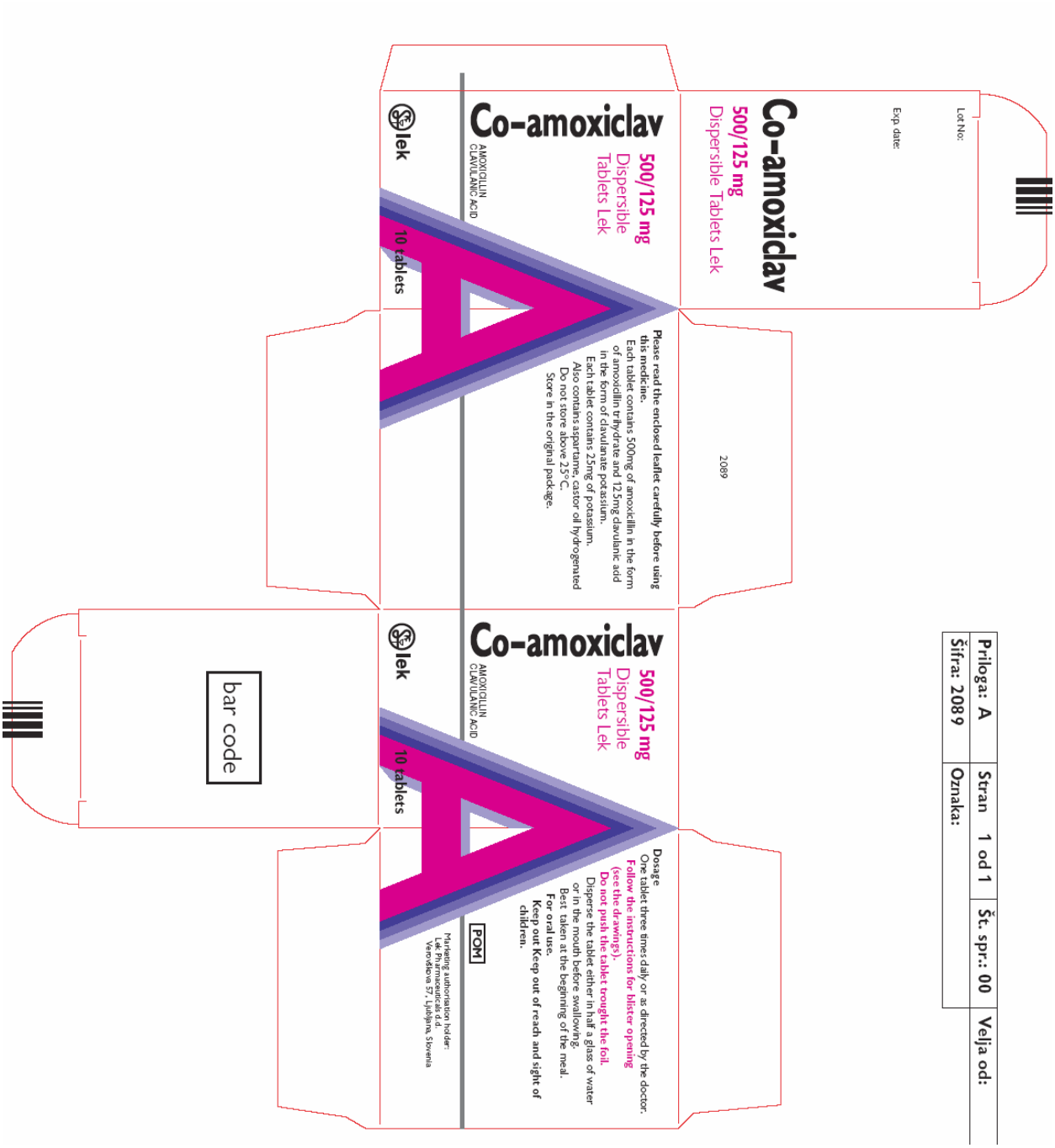
AMOXICILLIN
CLAVULANIC ACID
lek



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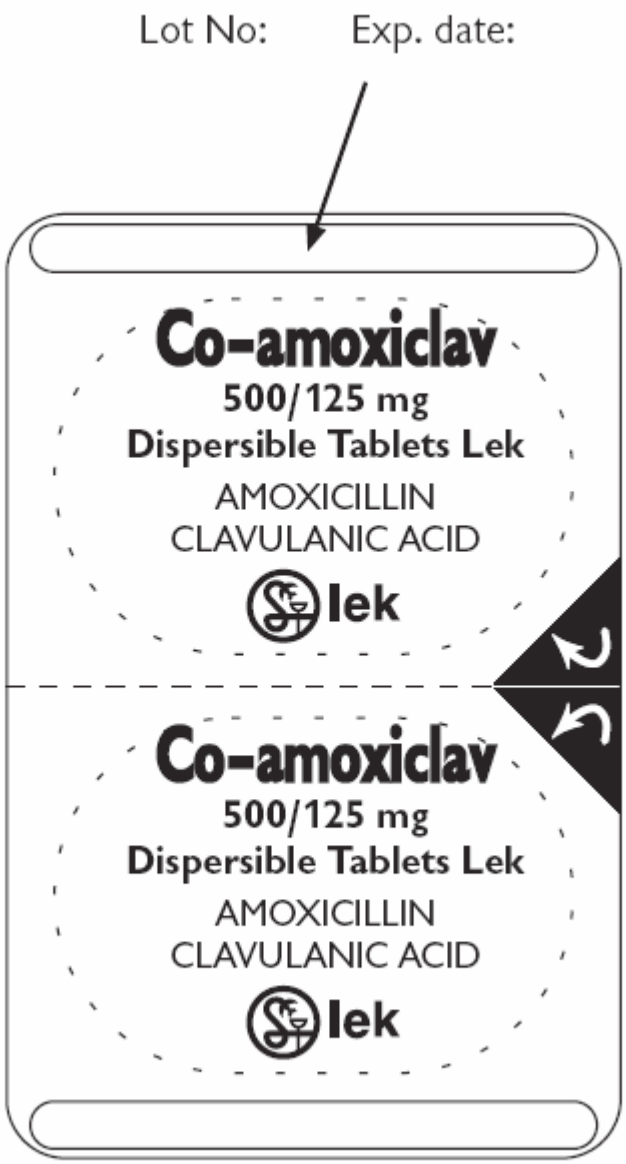
Šifra: 2089	Oznaka:		


Lot No:
Exp. date:
Co-amoxiclav
500/125 mg
Dispersible Tablets Lek
AMOXICILLIN
CLAVULANIC ACID
lek
Co-amoxiclav
500/125 mg
Dispersible Tablets Lek
AMOXICILLIN
CLAVULANIC ACID
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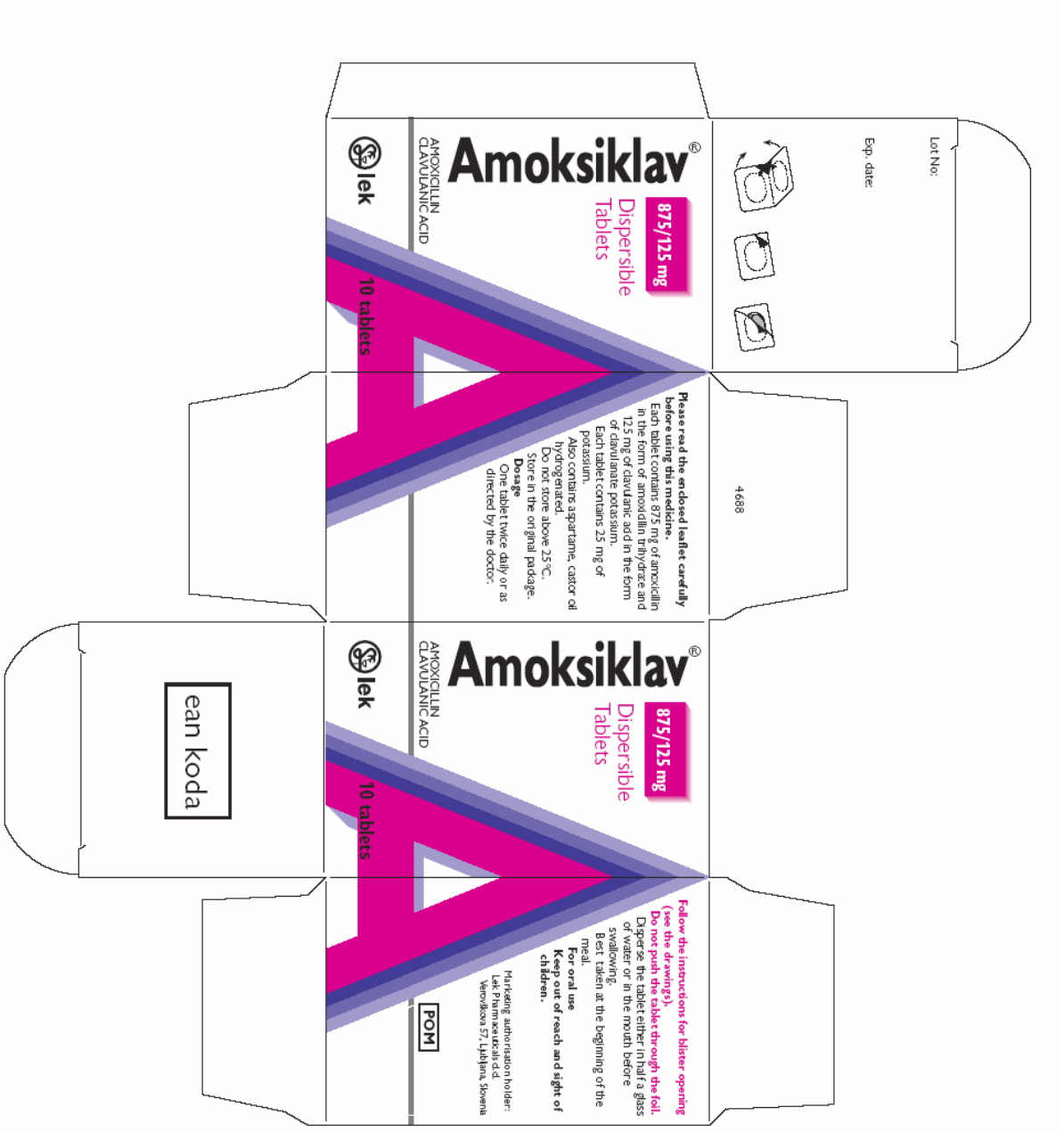
Lot No:
Exp. date:
4688
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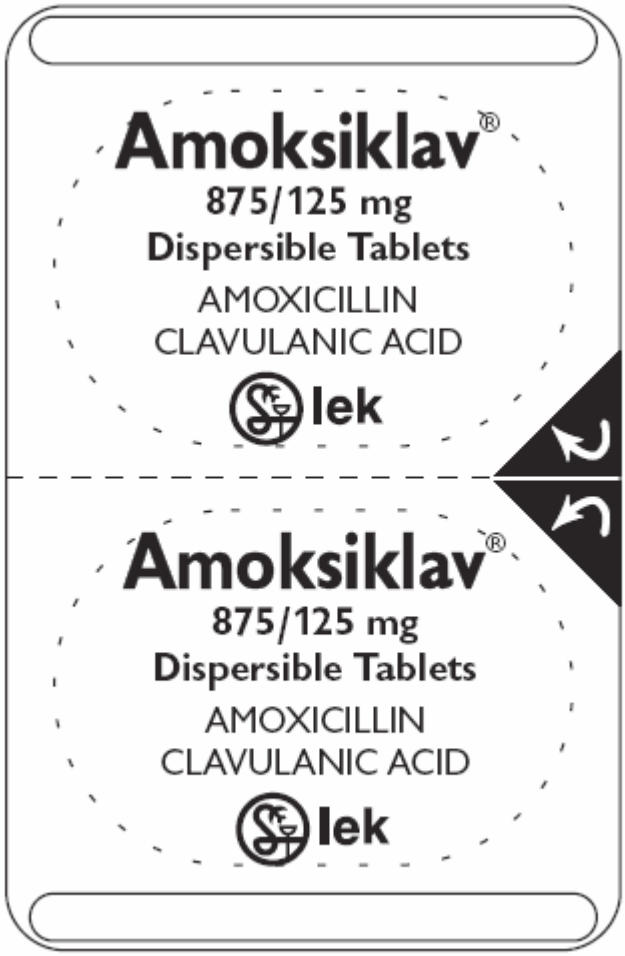
Each tablet contains 875 mg of amoxicillin in the form of amoxicillin trihydrate and 125 mg of clavulanic acid in the form of clavulanate potassium.
Each tablet contains 25 mg of potassium.
Also contains aspartame, castor oil hydrogenated.
Do not store above 25°C.
Store in the original package.
Dosage
One tablet twice daily or as directed by the doctor.
Amoksiklav®
AMOXICILLIN CLAVULANIC ACID
875/125 mg
Dispersible Tablets
10 tablets
lek
Follow the instructions for blister opening (see the drawings).
Do not push the tablet through the foil.
Disperse the tablet either in half a glass of water or in the mouth before swallowing.
Best taken at the beginning of the meal.
For oral use
Keep out of reach and sight of children.
Marketing authorisation holder:
Lek Pharmaceuticals d.d.
Verovškova 57, Ljubljana, Slovenia
POM
ean koda


Amoksiklav®
875/125 mg
Dispersible Tablets
AMOXICILLIN
CLAVULANIC ACID
lek
Amoksiklav®
875/125 mg
Dispersible Tablets
AMOXICILLIN
CLAVULANIC ACID
lek


Lot No:
Exp. date:
4689
Amoksiklav®
500/125 mg
Dispersible
Tablets
AMOXICILLIN
CLAVULANIC ACID
lek
10 tablets
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Also contains aspartame, castor oil hydrogenated
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Dosage
One tablet three times daily or as directed by doctor.
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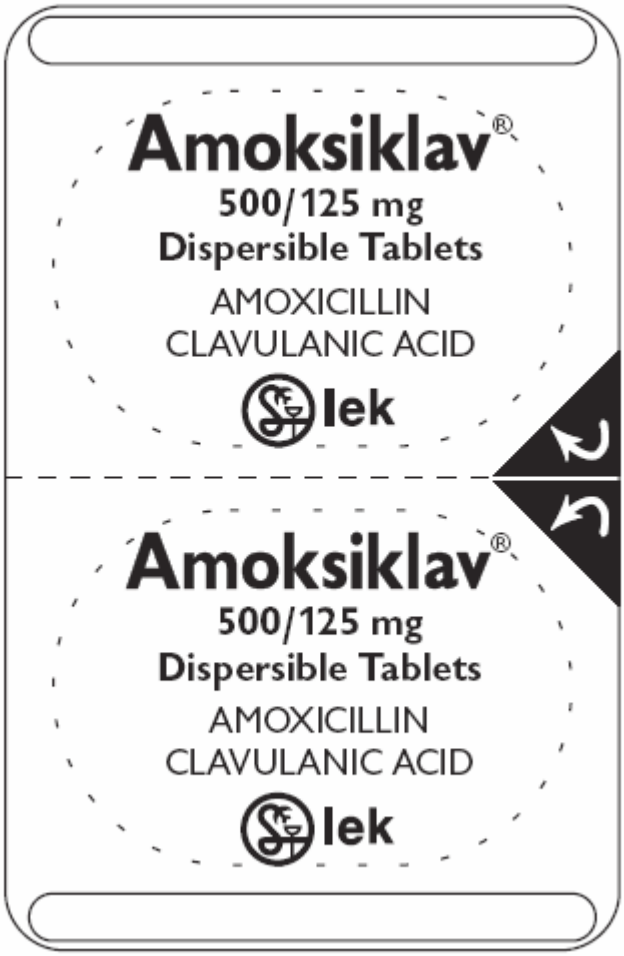
Amoksiklav®
500/125 mg
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