TABLE OF CONTENTS

Lay Summary
Scientific discussion
Steps taken for assessment
Summary of Product Characteristics
Product Information Leaflet
Labelling

Page 2
Page 3
Page 15
Riclasip® 200/28.5mg Granules for Oral Suspension  
PL 21727/0018

Riclasip® 300/42.75mg Granules for Oral Suspension  
PL 21727/0019

Riclasip® 400/57mg Granules for Oral Suspension  
PL 21727/0020

Co-amoxiclav DST Grunenthal 200/28.5 mg Granules for Oral Suspension  
PL 21727/0021

Co-amoxiclav DST Grunenthal 300/42.75 mg Granules for Oral Suspension  
PL 21727/0022

Co-amoxiclav DST Grunenthal 400/57 mg Granules for Oral Suspension  
PL 21727/0023

LAY SUMMARY

The MHRA has granted Grunenthal Limited Marketing Authorisations (licences) for the medicinal products Riclasip® 200/28.5mg Granules for oral suspension, Riclasip® 300/42.75mg Granules for oral suspension, Riclasip® 400/57mg Granules for oral suspension, Co-amoxiclav DST Grunenthal 200/28.5mg Granules for oral suspension, Co-amoxiclav DST Grunenthal 300/42.75mg Granules for oral suspension, and Co-amoxiclav DST Grunenthal 400/57mg Granules for oral suspension. (PL 21727/0018-23). These are prescription-only medicines (POM).

Riclasip®/Co-amoxiclav DST Grunenthal is an antibiotic for treating infections. It belongs to a group of antibiotics called “penicillins”. Riclasip®/Co-amoxiclav DST Grunenthal works by killing the bacteria that can cause infections.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Riclasip® 200/28.5mg Granules for oral suspension, Riclasip® 300/42.75mg Granules for oral suspension, Riclasip® 400/57mg Granules for oral suspension, Co-amoxiclav DST Grunenthal 200/28.5mg Granules for oral suspension, Co-amoxiclav DST Grunenthal 300/42.75mg Granules for oral suspension, and Co-amoxiclav DST Grunenthal 400/57mg Granules for oral suspension outweigh the risks, hence a Marketing Authorisations have been granted.
Riclasip® 200/28.5mg Granules for Oral Suspension
PL 21727/0018

Riclasip® 300/42.75mg Granules for Oral Suspension
PL 21727/0019

Riclasip® 400/57mg Granules for Oral Suspension
PL 21727/0020

Co-amoxiclav DST Grunenthal 200/28.5 mg Granules for Oral Suspension
PL 21727/0021

Co-amoxiclav DST Grunenthal 300/42.75 mg Granules for Oral Suspension
PL 21727/0022

Co-amoxiclav DST Grunenthal 400/57 mg Granules for Oral Suspension
PL 21727/0023

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>4</td>
</tr>
<tr>
<td>Pharmaceutical assessment</td>
<td>5</td>
</tr>
<tr>
<td>Preclinical assessment</td>
<td>8</td>
</tr>
<tr>
<td>Clinical assessment (including statistical assessment)</td>
<td>9</td>
</tr>
<tr>
<td>Overall conclusions and risk benefit assessment</td>
<td>14</td>
</tr>
</tbody>
</table>
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, marketing authorisations for the medicinal products Riclasip® 200/28.5mg Granules for oral suspension, Riclasip® 300/42.75mg Granules for oral suspension, Riclasip® 400/57mg Granules for oral suspension, Co-amoxiclav DST Grunenthal 200/28.5mg Granules for oral suspension, Co-amoxiclav DST Grunenthal 300/42.75mg Granules for oral suspension, and Co-amoxiclav DST Grunenthal 400/57mg Granules for oral suspension (PL 21727/0018-23) were granted on 9th May 2007. These products are prescription-only medicines (POM).

These are national, standard, abridged applications submitted under Article 10.1 first paragraph of Directive 2001/83/EC as amended. The reference product is Augmentin®-Duo 400/57 dry powder for reconstitution, first authorised to SmithKline Beecham plc (now GSK) on 23/10/1995 (PL 10592/0070).

Co-amoxiclav DST Grünenthal granules for oral suspension and Riclasip® Granules for oral suspension contain actives 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. The proposed indications include upper & lower respiratory tract infections, urinary tract infections and skin and soft tissue infections.

Riclasip® and Co-amoxiclav DST Grünenthal 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).
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nomenclature

rINN: Amoxicillin

Structure

A white or almost white, crystalline powder, slightly soluble in water, very slightly soluble in alcohol, practically insoluble in fatty oils. It dissolves in dilute acids and dilute solutions of alkali hydroxides.

rINN: Clavulanic acid

Structure

White or almost white, crystalline powder, hygroscopic. Freely soluble in water, slightly soluble in alcohol, very slightly soluble in acetone.

A valid Certificate of Suitability has been provided.

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

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

The active ingredients, amoxicillin and clavulanic acid are stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.
Batch analysis data are provided and comply with the proposed specification.

An acceptable justification of the proposed specifications has been provided.

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

Appropriate stability data have been generated supporting a retest period of 3 years for amoxicillin and 2 years for clavulanic acid.

**DRUG PRODUCT**

**Other ingredients**

Other ingredients consist of pharmaceutical excipients, namely Carrageenan, Calcium Phosphate Polysorbate 80, Triethyl citrate, Sucrose fatty acid ester, Kaolin Heavy, Methacrylic acid-ethyl acrylate copolymer 1:1 dispersion 30% and glycerol monostearate 40-55. All excipients used comply with their respective European Pharmacopoeia monograph or the US National formulary with the exception of Sucrose fatty acid ester which complies with the Japanese Pharmacopoeia.

Satisfactory specifications and Certificates of Analysis have been provided for all excipients. No materials of animal or human origin are contained in or used in the manufacture of this product.

No novel excipients are contained in the drug product and none are of human or animal original.

**Pharmaceutical development**

The objective of the pharmaceutical development programme was to produce products containing amoxicillin/clavulanic acid that are tolerable and which could be considered as generic products to the originator products Augmentin®-Duo 400/57 dry powder for reconstitution.

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

The rationale and function of each excipient added is discussed. Levels of each ingredient are typical for a product of this nature and have been optimised on the basis of results from development studies.

**Dissolution and Impurity profiles**

Dissolution and impurity profiles for all three strengths of drug product were found to be similar to the originator products. The data demonstrate that the dissolution specification is acceptable.

**Manufacture**

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches. The results are satisfactory.
Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System
Product is packaged in a drinking straw comprising a) the straw made of polypropylene, b) the cap made of polyolefin and c) the controller made of co-extruded polyolefin/polyolefin or polyester/polyolefin fibres. The drinking straw with the pellets is finally packaged in an aluminium sachet. Specifications and Certificates of Analysis for all packaging used have been provided. This is satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years and storage conditions of “Do not store above 25 degree C” and “Store in the original sachets” have been set, which is satisfactory.

Conclusion

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study. Bio-analytical methods used have been satisfactorily validated. Satisfactory bioequivalence is seen between the test and reference product.

SPC, PIL, Labels
The SPC, PIL and Labels are pharmaceutically acceptable.

The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Conclusion
The proposed product has been shown to be a generic medicinal product of the reference product and has met the requirements with respect to qualitative and quantitative content of the active substance. It is recommended that Marketing Authorisations should be granted for these applications.
PRECLINICAL ASSESSMENT

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

1. INTRODUCTION
These are national abridged applications in duplicate for Marketing Authorisations for Riclasip® Granules for Oral Suspension and Co-amoxiclav DST Grunenthal Granules for Oral Suspension in three dose of 200/28.5mg, 300/42.75mg, 400/57mg. The applications are submitted by Grunenthal Ltd under EC Article 10.1 of Directive 2001/83/EEC. The applicant is claiming that these are generic medicinal products of the UK innovator product Augmentin® -Duo 400/57, 400mg amoxicillin and 57 mg clavulanic acid, dry powder for reconstitution in water granted to GlaxoSmithKline and first authorised in the UK on 23rd September 1995 (PL 10592/0070).

2. BACKGROUND
Amoxicillin/clavulanic acid, ATC coded J01CR02, is an antibacterial combination consisting of the semi synthetic antibiotic amoxicillin and the ß-lactamase inhibitor clavulanic acid. Amoxicillin/Clavulanic acid is used in the EU and rest of the world for the treatment of respiratory tract infections, acute otitis media, and skin and soft tissue infections due to its good clinical and safety profile for more than 20 years. As these applications cover only a different formulation for an already known pharmaceutical form of amoxicillin/clavulanic acid a detailed evaluation of the environmental risk for this well-known drug substance is considered as no necessary.

Amoxicillin/clavulanic acid has the same qualitative and quantitative composition in terms of active principle as the originator product (Augmentin® -Duo 400/57, powder for oral suspension) in UK.
Amoxicillin/Clavulanic acid contains different excipients to the original GlaxoSmithKline product. However all of the excipients are well-known pharmacopoeia excipients. There are no excipients included in the composition which would raise any safety issues.

3. INDICATIONS
The indications as proposed in the SPC are similar to the innovator product, and are therefore acceptable.

4. DOSE & DOSE SCHEDULE
The dose and regimen as proposed in the SPC are identical to the brand leader/reference product, and are therefore acceptable.

5. TOXICOLOGY
The toxicology of Riclasip® and co-amoxiclav is well established. No toxicology data is required to be submitted for these types of applications.

6. CLINICAL PHARMACOLOGY

6.1 Pharmaceutics
Riclasip®/Co-amoxiclav contains different excipients to the original GlaxoSmithKline product. It only contains pharmacopoeia excipients. No non-clinical or clinical studies have been carried out on amoxicillin/clavulanic acid, apart from the volunteer bioequivalence study. However all of the excipients are
well-known pharmacopoeial excipients. There are no excipients included in the composition which would raise any safety issues.

6.2. Bioequivalence of the Grünenthal product to the GlaxoSmithKline product

The applicant presented 2 bioequivalence studies comparing the applicant formulation with the innovator Glaxo Smith Kline (GSK) reference product (Study HPDSTAC7/01) and with another reference GSK suspension with the same amount of excipients as the applicant product.

The applicant supplied a single bioequivalence study comparing the test product to the reference. A second bioequivalence trial compared a different formulation of the test product to a French licensed Augmentin sachet.

TRIAL HP DSTAC7/01

This was a randomised, open-label, single-dose, two-way crossover trial in fasted male healthy volunteers.

The treatments compared were:

Test - 2 straws of the applicant’s 400/57mg granules for oral suspension (test) corresponding to 800 mg amoxicillin and 114 mg clavulanic acid.

Reference – 10 ml of reconstituted Augmentin-Duo 400/57 (per 5ml) powder for oral suspension, manufactured by GlaxoSmithKline, corresponding to 800 mg amoxicillin and 114 mg clavulanic acid.

Volunteers received both treatments in a randomised order in each of two study periods, the periods being separated by a washout period of at least 2 days. Blood samples were taken pre-dose and at 0.17, 0.25, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 6, 8, 10 and 12 hours after dosing.

Results

The percentage of AUC_{0-\infty} of amoxicillin which was extrapolated was less than 20% for all subjects on both treatments. In fact the extrapolation was very small, being <1% for the vast majority of subjects. For clavulanic acid there were only 3 subjects for whom the extrapolation was >20%, 2 on the test product and 1 on the reference. This suggests that the sampling schedule was sufficient to characterise the concentration curves.

Plasma levels were below the limit of quantification at the start of period 2 for all subjects, indicating that the washout period was of an adequate duration.

The results from the 47 analysed subjects are shown in the table below. The data were analysed using ANOVA on log-transformed data with terms for sequence, subject within sequence, period and treatment. This is the analysis specified in the CHMP bioequivalence guideline.
Amoxicillin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Reference</th>
<th>Ratio: Test/Reference</th>
<th>Point estimate</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-t (mg-h/l)</td>
<td>33.58</td>
<td>34.59</td>
<td>0.97</td>
<td>0.95-0.99</td>
<td></td>
</tr>
<tr>
<td>AUC0-∞ (mg-h/l)</td>
<td>33.83</td>
<td>34.86</td>
<td>0.97</td>
<td>0.95-0.99</td>
<td></td>
</tr>
<tr>
<td>Cmax (mg/l)</td>
<td>13.04</td>
<td>13.59</td>
<td>0.96</td>
<td>0.92-1.00</td>
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</table>

Clavulanic acid

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<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Reference</th>
<th>Ratio: Test/Reference</th>
<th>Point estimate</th>
<th>90% CI</th>
</tr>
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<tr>
<td>AUC0-t (mg-h/l)</td>
<td>4.65</td>
<td>5.32</td>
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<tr>
<td>AUC0-∞ (mg-h/l)</td>
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<tr>
<td>Cmax (mg/l)</td>
<td>2.32</td>
<td>2.73</td>
<td>0.85</td>
<td>0.77-0.94</td>
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</tr>
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</table>

**TRIAL HP DSTAC8/01**

This was a randomised, open-label, single-dose, two-way crossover trial of identical design to HP DSTAC7/01.

The treatments compared were:

Test - 2 straws of the applicant’s 500/62.5mg granules for oral suspension (test) corresponding to 1000 mg amoxicillin and 125 mg clavulanic acid.

Reference – 2 sachets of Augmentin 500/62.5mg powder for oral suspension, manufactured by GlaxoSmithKline France, corresponding to 1000 mg amoxicillin and 125 mg clavulanic acid.

**Results**

The percentage of AUC0-∞ which was extrapolated was less than 20% for all subjects on both treatments for both amoxicillin and clavulanic acid suggesting that the sampling schedule was sufficient to characterise the concentration curves.

Plasma levels were below the limit of quantification at the start of period 2 for all subjects, indicating that the washout period was of an adequate duration.

The results are shown in the tables below.

Amoxicillin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Geometric mean</th>
<th>Ratio: Test/Reference</th>
<th>Point estimate</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-t (mg-h/l)</td>
<td>41.73</td>
<td>42.36</td>
<td>0.99</td>
<td>0.95-1.02</td>
</tr>
<tr>
<td>AUC0-∞ (mg-h/l)</td>
<td>42.10</td>
<td>42.71</td>
<td>0.99</td>
<td>0.96-1.02</td>
</tr>
<tr>
<td>Cmax (mg/l)</td>
<td>15.86</td>
<td>15.69</td>
<td>1.01</td>
<td>0.95-1.02</td>
</tr>
</tbody>
</table>

Clavulanic acid

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Geometric mean</th>
<th>Ratio: Test/Reference</th>
</tr>
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<tbody>
<tr>
<td>Parameter</td>
<td>Test</td>
<td>Reference</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------</td>
<td>-----------</td>
</tr>
<tr>
<td>$AUC_{0-t}$ (mg-h/l)</td>
<td>5.15</td>
<td>5.32</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$ (mg-h/l)</td>
<td>5.58</td>
<td>5.73</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (mg/l)</td>
<td>2.50</td>
<td>2.56</td>
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</table>

Assessor’s Comments on Overage.

The justification for the low CIs for the points estimates on the basis of unequal overage is logical but to show bioequivalence of these parameters another formulation without extra overage is essentially logical but invalid as this is not the reference product and therefore the reference does not comply with the NFG. However, the PA has established that this second reference formulation used in bioequivalence study HP DSTAC7/01 is essentially qualitatively the same as the test formulation and also that there is definitely an overage in the UK reference product, then this study HP DSTAC8/01 is acceptable as supportive data for Study HP DSTAC7/01.

Assessor’s Comment on bioequivalence of other doses.

No bioequivalence study was conducted or data submitted for the other doses. The use of only one dose strength of amoxicillin/clavulanic acid in this bioequivalence study is justified in the Clinical Summary/Overview because the pharmacokinetics of amoxicillin and clavulanic acid are linear. The DST formulation containing 400/57 mg of active ingredients is composed of the same granules as the 200/28.5 mg dose and the 300/42.9 mg dose. The qualitative composition of the granules and the ratio between the amounts of active substance and excipients is identical for the three amoxicillin/clavulanic acid-DST dose strengths. Therefore, the results of this bioequivalence study performed with the 400/57 mg dose strength are also applicable to the 200/28.5 mg and the 300/42.9 mg dose strengths.

7. **EFFICACY**

The efficacy of Riclasip® /Co-amoxiclav is well established. No new efficacy data is required for these applications.

8. **SAFETY**

The safety of Riclasip® /Co-amoxiclav is well established. No new safety data is required for these applications.

Amoxicillin/Clavulanic acid-DST contains different excipients to the original GlaxoSmithKline product. However all of the excipients are well-known pharmacopeial excipients. There are no excipients included in the composition which would raise any safety issues. Therefore no non-clinical or clinical studies have been carried out on amoxicillin/clavulanic acid-DST, apart from the volunteer bioequivalence study.

9. **EXPERT REPORTS**

The clinical expert report has been written by an appropriately qualified medic. It is an adequate summary of the clinical data provided in the dossier.
14. DISCUSSION
Amoxicillin/clavulanic acid-DST has the same qualitative and quantitative composition in terms of active principle as the originator product (Augmentin®-Duo 400/57, powder for oral suspension) in UK. Although the PK parameters in the pivotal bioequivalence study DSTAC7/01 were different for clavulanic acid, these differences were explained by the lack of overage in the test vs the reference product. A second bioequivalence study DSTAC8/01 HP was carried out using as reference Augmentin® sachet, 500/62.5, FR which does not contain an excess of clavulanic acid. This was shown to be bioequivalent to the test product, thereby providing supporting evidence that lower result for clavulanic acid in study DSTAC7/01, was due to the lack of overage in the applicant product vs. the UK innovator reference product, (Augmentin®-Duo 400/57, powder for oral suspension)

15. RECOMMENDATION
Marketing authorisations should be granted.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Riclasip®/Co-amoxiclav DST Grunenthal Granules for oral suspension 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 application of this type.

EFFICACY
The efficacy of Riclasip®/Co-amoxiclav has been well documented in the past.

No new or unexpected safety concerns arise from these applications.

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

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The benefit/risk balance is considered to be positive.
Riclasip® 200/28.5mg Granules for Oral Suspension
PL 21727/0018

Riclasip® 300/42.75mg Granules for Oral Suspension
PL 21727/0019

Riclasip® 400/57mg Granules for Oral Suspension
PL 21727/0020

Co-amoxiclav DST Grunenthal 200/28.5 mg Granules for Oral Suspension
PL 21727/0021

Co-amoxiclav DST Grunenthal 300/42.75 mg Granules for Oral Suspension
PL 21727/0022

Co-amoxiclav DST Grunenthal 400/57 mg Granules for Oral Suspension
PL 21727/0023

**STEPS TAKEN FOR ASSESSMENT**

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<table>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 13th October 2005</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 7th November 2005</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information relating to the quality dossier on 15th June 2006</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s request, providing further information on the quality section on 25th September 2006</td>
</tr>
<tr>
<td>5</td>
<td>The application was determined on 9th May 2007</td>
</tr>
</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Riclasip® 200/28.5 mg granules for oral suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Riclasip 200/28.5 mg granules for oral suspension:
Each drinking straw with 408.6 mg granules for oral suspension contains 200 mg amoxicillin (present as amoxicillin trihydrate) and 28.5 mg clavulanic acid (present as potassium clavulanate)

For excipients, see section 6.1

3 PHARMACEUTICAL FORM
Granules for oral suspension.

White to yellowish granules (amoxicillin) and yellowish to greyish granules (clavulanic acid).

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS
Riclasip granules for oral suspension is an antibiotic agent with a notably broad spectrum of activity against the commonly occurring bacterial pathogens in general practice and hospital. The β-lactamase inhibitory action of clavulanate extends the spectrum of amoxicillin to embrace a wider range of organisms, including many resistant to other β-lactam antibiotics.

Riclasip granules for oral suspension, for twice-daily (b.i.d) oral dosing, is indicated for short-term treatment of bacterial infections at the following sites when amoxicillin resistant β-lactamase-producing strains are suspected as the cause. In other situations, amoxicillin alone should be considered.
- Upper Respiratory Tract Infections (including ENT) in particular sinusitis, otitis media, recurrent tonsillitis. These infections are often caused by Streptococcus pneumoniae, Haemophilus influenzae*, Moraxella catarrhalis* and Streptococcus pyogenes.
- Lower Respiratory Tract Infections in particular acute exacerbations of chronic bronchitis (especially if considered severe), bronchopneumonia. These infections are often caused by Streptococcus pneumoniae, Haemophilus influenzae* and Moraxella catarrhalis*.
- Urinary Tract Infections in particular cystitis (especially when recurrent or complicated - excluding prostatitis). These infections are often caused by Enterobacteriaceae* (mainly Escherichia coli*), Staphylococcus saprophyticus, Enterococcus species.*
- Skin and Soft Tissue Infections in particular cellulitis, animal bites and severe dental abscess with spreading cellulitis. These infections are often caused by Staphylococcus aureus*, Streptococcus pyogenes and Bacteroides species*.
- A comprehensive list of sensitive organisms is provided in Section 5.
* Some members of these species of bacteria produce β-lactamase, rendering them insensitive to amoxicillin alone.

Mixed infections caused by amoxicillin-susceptible organisms in conjunction with Riclasip granules for oral suspension -susceptible β-lactamase-producing organisms may be treated with Riclasip granules for oral suspension. These infections should not require the addition of another antibiotic resistant to β-lactamases.

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**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Weight Range</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 - 6 years</td>
<td>13 - 21 kg</td>
<td>200/28.5 mg Riclasip granules for oral suspension b.i.d.</td>
</tr>
<tr>
<td>7 – 9 years</td>
<td>22 – 31 kg</td>
<td>300/42.75 mg Riclasip granules for oral suspension b.i.d.</td>
</tr>
<tr>
<td>10 - 12 years</td>
<td>32 - 40 kg</td>
<td>400/57 mg (or 2x 200/28.5 mg) Riclasip granules for oral suspension b.i.d.</td>
</tr>
<tr>
<td>2 - 6 years</td>
<td>13 - 21 kg</td>
<td>400/57 mg (or 2x 200/28.5 mg) Riclasip granules for oral suspension b.i.d.</td>
</tr>
<tr>
<td>7 – 9 years</td>
<td>22 – 31 kg</td>
<td>2x 300/42.75 mg Riclasip granules for oral suspension b.i.d.</td>
</tr>
<tr>
<td>10 - 12 years</td>
<td>32 - 40 kg</td>
<td>2x 400/57 mg Riclasip granules for oral suspension b.i.d.</td>
</tr>
</tbody>
</table>

Riclasip granules for oral suspension are not suitable for patients incapable of using an ordinary drinking straw (e.g. children younger than 2 years). These patients should use other forms of co-amoxiclav.

**Infants with immature kidney function**

For children with immature renal function Riclasip granules for oral suspension is not recommended.

**Renal impairment**

For patients with a GFR of >30 ml/min no adjustment in dosage is required. For patients with a GFR of ≤30 ml/min Riclasip granules for oral suspension 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.

**Riclasip granules for oral suspension should be used according to the instructions below.**
Riclasip granules for oral suspension straws are sealed in sachets for single-use. Immediately before use, the sachet is to be torn at the upper notch and pulled down. When handling the straw, damage by pinching and squashing must be avoided.

The straw is taken out of the sachet sideways keeping it upright (the cap should be at the top).

The cap is pulled upwards. The straw should not be turned upside-down. Care must be taken not to spill any of the contained granules.

The lower end of the straw containing a white “controller” is put into a suitable drink. Suitable drinks are clear fluids (hot beverages above 40 °C should be avoided) which are not viscous or containing solid particles, e.g. lemonades, fruit juices (without pulp), homogenised milk (up to 3.5% fat), tea or water. Carbonated drinks should be preferred as these can mask the sensation in the mouth caused by the granules. Full-fat milk (> 3.5% fat), milk-shakes or drinks with particles should not be used as they may clog the straw.

The drink is sipped through the straw. During sipping, the granules are dispersed. Riclasip granules for oral suspension straws contain a single dose of co-amoxiclav, all of which is to be taken at the same time. Several sips may be required to complete the dose.

Biting the granules should be avoided.

Chewing and biting on the straw should be avoided.

During sipping, the granules are dispersed and the white controller moves upwards, however, it remains in the straw. The controller is not part of the medication. Finally, an adequate amount of beverage should be drunk and remaining granules should be swallowed by flushing the mouth with the drink.

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Changes in liver function tests have been observed in some patients receiving co-amoxiclav. The clinical significance of these changes is uncertain but co-amoxiclav should be used with caution in patients with evidence of hepatic dysfunction.

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

In patients with mild renal impairment (GFR > 30 ml/min), no dosage adjustment is needed (see Section 4.2) In patients with moderate or severe renal impairment (GFR ≤ 30 ml/min) Riclasip granules for oral suspension is not recommended.

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria (see Section 4.9 Overdose).

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity (see Section 4.3).

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

Prolonged use may also occasionally result in overgrowth of non-susceptible organisms.

This medicinal product contains sucrose ester which might be a source of sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. The maximum amount of sucrose that might be formed out the sucrose ester is 3.5 – 7 mg per straw, depending on the strength.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Prolongation of bleeding time and prothrombin time have been reported in some patients receiving co-amoxiclav. Co-amoxiclav should be used with care in patients on anti-coagulation therapy. In common with other broad-spectrum antibiotics, co-amoxiclav may reduce the efficacy of oral contraceptives and patients should be warned accordingly.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. There are no data on the concomitant use of co-amoxiclav and allopurinol.

4.6 PREGNANCY AND LACTATION
Use in pregnancy
Reproduction studies in animals (mice and rats) with orally and parenterally administered co-amoxiclav have shown no teratogenic effects. In a single study in women with preterm, premature rupture of the foetal membrane (pPROM), it was reported that prophylactic treatment with co-amoxiclav may be associated with an increased risk of necrotising enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the physician.

Use in lactation
Co-amoxiclav may be administered during the period of lactation. With the exception of the risk of sensitisation, associated with the excretion of trace quantities in breast milk, there are no known detrimental effects for the breast-fed infant.
4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Adverse effects on the ability to drive or operate machinery have not been observed.

4.8 UNDESIRABLE EFFECTS
Side effects are uncommon and mainly of a mild and transitory nature.

Gastrointestinal reactions:
Diarrhoea, indigestion, nausea, vomiting, and mucocutaneous candidiasis have been reported. Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) has been reported rarely. Nausea, although uncommon, is more often associated with higher oral dosages. If gastrointestinal side effects occur with oral therapy they may be reduced by taking co-amoxiclav at the start of meals. Superficial tooth discolouration has been reported rarely, mostly with the suspension. It can usually be removed by brushing.

Renal and urinary tract disorders:
Crystalluria has been reported very rarely (see Section 4.9 Overdose).

Genito-urinary effects:
Vaginal itching, soreness and discharge may occur.

Hepatic effects:
Moderate and asymptomatic rises in AST and/or ALT and alkaline phosphatases have been reported occasionally. Hepatitis and cholestatic jaundice have been reported rarely. These hepatic reactions have been reported more commonly with co-amoxiclav than with other penicillins. After co-amoxiclav hepatic reactions have been reported more frequently in males and elderly patients, particularly those over 65 years. The risk increases with duration of treatment longer than 14 days. These reactions have been very rarely reported in children.

Signs and symptoms usually occur during or shortly after treatment but in some cases may not occur until several weeks after treatment has ended. Hepatic reactions are usually reversible but they may be severe and, very rarely, deaths have been reported.

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

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

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

4.9 OVERDOSE
Overdosage:
Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. They may be treated symptomatically, with attention to the water/electrolyte balance. Co-amoxiclav may be removed from the circulation by haemodialysis.
Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see Section 4.4 Special warnings and special precautions for use)

**Drug abuse and dependence:**
Drug dependency, addiction and recreational abuse have not been reported as a problem with this compound.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Riclasip granules for oral suspension contains a combination of amoxicillin and clavulanic acid, co-amoxiclav.

Pharmacotherapeutic group: Amoxicillin and enzyme inhibitors.

ATC code: J01CR02

**Microbiology**
Amoxicillin is a semi-synthetic antibiotic with a broad spectrum of antibacterial activity against many Gram-positive and Gram-negative micro-organisms. Amoxicillin is, however, susceptible to degradation by β-lactamases and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a β-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of β-lactamase enzymes commonly found in micro-organisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid mediated beta-lactamases frequently responsible for transferred drug resistance. It is generally less effective against chromosomally-mediated type 1 β-lactamases.

The presence of clavulanic acid in Riclasip granules for oral suspension protects amoxicillin from degradation by β-lactamase enzymes and effectively extends the antibacterial spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other penicillins and cephalosporins. Thus Riclasip granules for oral suspension possesses the distinctive properties of a broad spectrum antibiotic and a β-lactamase inhibitor. Riclasip granules for oral suspension is bactericidal to a wide range of organisms including:

**Gram-positive**
- Aerobes: *Enterococcus faecalis*, *Enterococcus faecium*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus*, *Coagulase negative staphylococci* (including *Staphylococcus epidermidis*), *Corynebacterium species*, *Bacillus anthracis*, *Listeria monocytogenes*.
- Anaerobes: *Clostridium species*, *Peptococcus species*, *Peptostreptococcus*.

**Gram-negative**
- Anaerobes: *Bacteroides species* including *B. fragilis*.

* Some members of these species of bacteria produce β-lactamase, rendering them insensitive to amoxicillin alone.

5.2 PHARMACOKINETIC PROPERTIES

**Absorption**
The two components of Riclasip granules for oral suspension, amoxicillin and clavulanic acid, are each fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption of co-amoxiclav is optimised when taken at the start of a meal.
Pharmacokinetics
Pharmacokinetic studies have been performed in children, including one study which has compared co-amoxiclav t.i.d and b.i.d. All of these data indicate that the elimination pharmacokinetics seen in adults also apply to children with mature kidney function.

The mean AUC values for amoxicillin are essentially the same following twice-a-day dosing with the 875/125 mg tablet or three-times-a-day dosing with the 500/125 mg tablet, in adults. No differences between the 875 mg bid and 500 mg t.i.d dosing regimes are seen when comparing the amoxicillin T½, or Cmax after normalisation for the different doses of amoxicillin administered. Similarly, no differences are seen for the clavulanate T½, Cmax or AUC values after appropriate dose normalisation.

The time of dosing of co-amoxiclav relative to the start of a meal has no marked effects on the pharmacokinetics of amoxicillin in adults. In a study of the 875/125 mg tablet, the time of dosing relative to ingestion of a meal had a marked effect on the pharmacokinetics of clavulanate. For clavulanate AUC and Cmax, the highest mean values and smallest inter-subject variabilities were achieved by administering co-amoxiclav at the start of a meal, compared to the fasting state or 30 or 150 minutes after the start of a meal.

The mean Cmax, Tmax, T½ and AUC values for amoxicillin and clavulanic acid are given below for an 800 mg/114 mg dose of co-amoxiclav that were administered to male subjects who fasted for at least 12 hours.

Mean Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Drug Administration</th>
<th>Dose (mg)</th>
<th>Cmax (mg/L)</th>
<th>Tmax (hours)</th>
<th>AUCl0-∞ (mg.h/L)</th>
<th>T½ (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riclasip granules for oral suspension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>800</td>
<td>13.04</td>
<td>1.25</td>
<td>33.83</td>
<td>1.33</td>
</tr>
<tr>
<td>Clavulanic acid</td>
<td>114</td>
<td>2.32</td>
<td>1.00</td>
<td>5.11</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* Median values

Amoxicillin serum concentrations achieved with co-amoxiclav are similar to those produced by the oral administration of equivalent doses of amoxicillin alone.

Distribution
Following intravenous administration therapeutic concentrations of both amoxicillin and clavulanic acid may be detected in the tissues and interstitial fluid. Therapeutic concentrations of both drugs have been found in gall bladder, abdominal tissue, skin, fat, and muscle tissues; fluids found to have therapeutic levels include synovial and peritoneal fluids, bile and pus.

Neither amoxicillin nor clavulanic acid is highly protein bound, studies show that about 25% for clavulanic acid and 18% for amoxicillin of total plasma drug content is bound to protein. From animal studies there is no evidence to suggest that either component accumulates in any organ.

Amoxicillin, like most penicillins, can be detected in breast milk. There are no data available on the passage of clavulanic acid into breast milk.

Reproduction studies in animals have shown that both amoxicillin and clavulanic acid penetrate the placental barrier. However, no evidence of impaired fertility or harm to the foetus was detected.

Elimination:
As with other penicillins, the major route of elimination for amoxicillin is via the kidney, whereas for clavulanate elimination is by both non-renal and renal mechanisms. Approximately 60-70% of the amoxicillin and approximately 40-65% of the clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of a single 375 or 625 mg tablet.

Amoxicillin is also partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to 10-25% of the initial dose. Clavulanic acid is extensively metabolised in man to 2,5-dihydro-4-(2-hydroxyethyl)-5-oxo-1H-pyrrole-3-carboxylic acid and 1-amino-4-hydroxy-butan-2-one and eliminated in urine and faeces and as carbon dioxide in expired air.

5.3 PRECLINICAL SAFETY DATA
No further information of relevance

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
sucrose ester (E 473)
kaolin heavy
triethyl citrate (E 1505)
Carrageenan (E 407)
methacrylic acid ethylacrylate copolymer 1:1 dispersion
calcium phosphate (E 341)
glycerol monostearate (E471)
polysorbate 80 (E 433)

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 sachets
Do not pinch or squash the straws

6.5 NATURE AND CONTENTS OF CONTAINER
Each aluminium sachet contains a blue translucent polypropylene straw that is sealed on one side by a polypropylene cap and on the other side by a polyester/polyolefin controller.

Pack sizes:
Cartons containing 2, 10, 14, 20, or 5x18 drinking straws.
Not all pack sizes may be marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Used straws can be put in household waste.

7 MARKETING AUTHORISATION HOLDER
Grüenthal Ltd.
Regus Lakeside House
1 Furzeground Way
Stockley Park East
Uxbridge UB11 1BD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 21727/0018
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
09/05/2007

10 DATE OF REVISION OF THE TEXT
09/05/2007
1 NAME OF THE MEDICINAL PRODUCT
Riclasip® 300/42.75 mg granules for oral suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Riclasip 300/42.75 mg granules for oral suspension:
Each drinking straw with 613 mg granules for oral suspension contains 300 mg amoxicillin (present as amoxicillin trihydrate) and 42.75 mg clavulanic acid (present as potassium clavulanate)

For excipients, see section 6.1

3 PHARMACEUTICAL FORM
Granules for oral suspension.

White to yellowish granules (amoxicillin) and yellowish to greyish granules (clavulanic acid).

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS
Riclasip granules for oral suspension is an antibiotic agent with a notably broad spectrum of activity against the commonly occurring bacterial pathogens in general practice and hospital. The β-lactamase inhibitory action of clavulanate extends the spectrum of amoxicillin to embrace a wider range of organisms, including many resistant to other β-lactam antibiotics.

Riclasip granules for oral suspension, for twice-daily (b.i.d) oral dosing, is indicated for short-term treatment of bacterial infections at the following sites when amoxicillin resistant β-lactamase-producing strains are suspected as the cause. In other situations, amoxicillin alone should be considered.

- **Upper Respiratory Tract Infections (including ENT)** in particular sinusitis, otitis media, recurrent tonsillitis. These infections are often caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* *, Moraxella catarrhalis* and *Streptococcus pyogenes*.

- **Lower Respiratory Tract Infections** in particular acute exacerbations of chronic bronchitis (especially if considered severe), bronchopneumonia. These infections are often caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* *.

- **Urinary Tract Infections** in particular cystitis (especially when recurrent or complicated - excluding prostatitis). These infections are often caused by *Enterobacteriaceae* (mainly *Escherichia coli* *), *Staphylococcus saprophyticus*, *Enterococcus* species.*

- **Skin and Soft Tissue Infections** in particular cellulitis, animal bites and severe dental abscess with spreading cellulitis. These infections are often caused by *Staphylococcus aureus*, *Streptococcus pyogenes* and *Bacteroides* species*.

- A comprehensive list of sensitive organisms is provided in Section 5. * Some members of these species of bacteria produce β-lactamase, rendering them insensitive to amoxicillin alone.

Mixed infections caused by amoxicillin-susceptible organisms in conjunction with Riclasip granules for oral suspension -susceptible β-lactamase-producing organisms may be treated with Riclasip granules for oral suspension. These infections should not require the addition of another antibiotic resistant to β-lactamases.

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**

<table>
<thead>
<tr>
<th>Weight Range</th>
<th>Dosage</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>25/3.6 mg/kg/day</td>
<td>2 - 6 years (13 - 21 kg)</td>
<td>200/28.5 mg Riclasip granules for oral suspension b.i.d.</td>
</tr>
<tr>
<td>45/6.4 mg/kg/day</td>
<td>2 - 6 years (13 - 21 kg)</td>
<td>400/57 mg (or 2x 200/28.5 mg) Riclasip granules for oral suspension b.i.d.</td>
</tr>
<tr>
<td></td>
<td>7 – 9 years (22 – 31 kg)</td>
<td>300/42.75 mg Riclasip granules for oral suspension b.i.d.</td>
</tr>
<tr>
<td></td>
<td>10 - 12 years (32 - 40 kg)</td>
<td>400/57 mg (or 2x 200/28.5 mg) Riclasip granules for oral suspension b.i.d.</td>
</tr>
<tr>
<td></td>
<td>7 – 9 years (22 – 31 kg)</td>
<td>2x 300/42.75 mg Riclasip granules for oral suspension b.i.d.</td>
</tr>
<tr>
<td></td>
<td>10 - 12 years (32 - 40 kg)</td>
<td>2x 400/57 mg Riclasip granules for oral suspension b.i.d.</td>
</tr>
</tbody>
</table>

Riclasip granules for oral suspension are not suitable for patients incapable of using an ordinary drinking straw (e.g. children younger than 2 years). These patients should use other forms of co-amoxiclav.

**Infants with immature kidney function**

For children with immature renal function Riclasip granules for oral suspension is not recommended.

**Renal impairment**

For patients with a GFR of >30 ml/min no adjustment in dosage is required. For patients with a GFR of ≤30 ml/min Riclasip granules for oral suspension 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.

**Riclasip granules for oral suspension should be used according to the instructions below.**

Riclasip granules for oral suspension straws are sealed in sachets for single-use. Immediately before use, the sachet is to be torn at the upper notch and pulled down. When handling the straw, damage by pinching and squashing must be avoided.
The straw is taken out of the sachet sideways keeping it upright (the cap should
be at the top).

The cap is pulled upwards. The straw should not be turned upside-down. Care
must be taken not to spill any of the contained granules.

The lower end of the straw containing a white “controller” is put into a suitable
drink.
Suitable drinks are clear fluids (hot beverages above 40 °C should be avoided)
which are not viscous or containing solid particles, e.g. lemonades, fruit juices
(without pulp), homogenised milk (up to 3.5% fat), tea or water. Carbonated
drinks should be preferred as these can mask the sensation in the mouth caused
by the granules. Full-fat milk (> 3.5% fat), milk-shakes or drinks with particles
should not be used as they may clog the straw.

The drink is sipped through the straw. During sipping, the granules are dispersed.
Riclasip granules for oral suspension straws contain a single dose of co-
amoxiclav, all of which is to be taken at the same time. Several sips may be
required to complete the dose.
Biting the granules should be avoided.
Chewing and biting on the straw should be avoided.

During sipping, the granules are dispersed and the white controller moves
upwards, however, it remains in the straw. The controller is not part of the
medication.
Finally, an adequate amount of beverage should be drunk and remaining granules
should be swallowed by flushing the mouth with the drink.

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Changes in liver function tests have been observed in some patients receiving co-amoxiclav.
The clinical significance of these changes is uncertain but co-amoxiclav should be used with
cautions in patients with evidence of hepatic dysfunction.
Cholestatic jaundice, which may be severe, but is usually reversible, has been reported rarely. Signs and symptoms may not become apparent for several weeks after treatment has ceased.

In patients with mild renal impairment (GFR > 30 ml/min), no dosage adjustment is needed (see Section 4.2). In patients with moderate or severe renal impairment (GFR ≤ 30 ml/min) Riclasip granules for oral suspension is not recommended.

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria (see Section 4.9 Overdose).

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity (see Section 4.3).

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

Prolonged use may also occasionally result in overgrowth of non-susceptible organisms.

This medicinal product contains sucrose ester which might be a source of sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. The maximum amount of sucrose that might be formed out the sucrose ester is 3.5 – 7 mg per straw, depending on the strength.

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Prolongation of bleeding time and prothrombin time have been reported in some patients receiving co-amoxiclav. Co-amoxiclav should be used with care in patients on anticoagulation therapy. In common with other broad-spectrum antibiotics, co-amoxiclav may reduce the efficacy of oral contraceptives and patients should be warned accordingly.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. There are no data on the concomitant use of co-amoxiclav and allopurinol.

4.6 PREGNANCY AND LACTATION

Use in pregnancy

Reproduction studies in animals (mice and rats) with orally and parenterally administered co-amoxiclav have shown no teratogenic effects. In a single study in women with preterm, premature rupture of the foetal membrane (pPROM), it was reported that prophylactic treatment with co-amoxiclav may be associated with an increased risk of necrotising enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the physician.

Use in lactation

Co-amoxiclav may be administered during the period of lactation. With the exception of the risk of sensitisation, associated with the excretion of trace quantities in breast milk, there are no known detrimental effects for the breast-fed infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Adverse effects on the ability to drive or operate machinery have not been observed.

4.8 UNDESIRABLE EFFECTS

Side effects are uncommon and mainly of a mild and transitory nature.

Gastrointestinal reactions:
Diarrhoea, indigestion, nausea, vomiting, and mucocutaneous candidiasis have been reported. Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) has been reported rarely. Nausea, although uncommon, is more often associated with higher oral dosages. If gastrointestinal side effects occur with oral therapy they may be reduced by taking co-amoxiclav at the start of meals. Superficial tooth discolouration has been reported rarely, mostly with the suspension. It can usually be removed by brushing.

_Renal and urinary tract disorders:_
Crystalluria has been reported very rarely (see Section 4.9 Overdose).

_Genito-urinary effects:_
Vaginal itching, soreness and discharge may occur.

_Hepatic effects:_
Moderate and asymptomatic rises in AST and/or ALT and alkaline phosphatases have been reported occasionally. Hepatitis and cholestatic jaundice have been reported rarely. These hepatic reactions have been reported more commonly with co-amoxiclav than with other penicillins. After co-amoxiclav hepatic reactions have been reported more frequently in males and elderly patients, particularly those over 65 years. The risk increases with duration of treatment longer than 14 days. These reactions have been very rarely reported in children.

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

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

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

### 4.9 OVERDOSE

_Overdosage:_
Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. They may be treated symptomatically, with attention to the water/electrolyte balance. Co-amoxiclav may be removed from the circulation by haemodialysis.

Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see Section 4.4 Special warnings and special precautions for use)

_Drug abuse and dependence:_
Drug dependency, addiction and recreational abuse have not been reported as a problem with this compound.
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Microbiology

Amoxicillin is a semi-synthetic antibiotic with a broad spectrum of antibacterial activity against many Gram-positive and Gram-negative micro-organisms. Amoxicillin is, however, susceptible to degradation by \( \beta \)-lactamases and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a \( \beta \)-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of \( \beta \)-lactamase enzymes commonly found in micro-organisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid mediated beta-lactamases frequently responsible for transferred drug resistance. It is generally less effective against chromosomally-mediated type 1 \( \beta \)-lactamases.

The presence of clavulanic acid in Riclasip granules for oral suspension protects amoxicillin from degradation by \( \beta \)-lactamase enzymes and effectively extends the antibacterial spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other penicillins and cephalosporins. Thus Riclasip granules for oral suspension possesses the distinctive properties of a broad spectrum antibiotic and a \( \beta \)-lactamase inhibitor. Riclasip granules for oral suspension is bactericidal to a wide range of organisms including:

**Gram-positive**

Aerobes: *Enterococcus faecalis*, *Enterococcus faecium*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus viridans*, *Staphylococcus aureus*, *Coagulase negative staphylococci* (including *Staphylococcus epidermidis*), *Corynebacterium species*, *Bacillus anthracis*, *Listeria monocytogenes*.

Anaerobes: *Clostridium species*, *Peptococcus species*, *Peptostreptococcus*.

**Gram-negative**


Anaerobes: Bacteroides species including *B. fragilis*.

* Some members of these species of bacteria produce \( \beta \)-lactamase, rendering them insensitive to amoxicillin alone.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

The two components of Riclasip granules for oral suspension, amoxicillin and clavulanic acid, are each fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption of co-amoxiclav is optimised when taken at the start of a meal.

Pharmacokinetics

Pharmacokinetic studies have been performed in children, including one study which has compared co-amoxiclav t.i.d and b.i.d. All of these data indicate that the elimination pharmacokinetics seen in adults also apply to children with mature kidney function.
The mean AUC values for amoxicillin are essentially the same following twice-a-day dosing with the 875/125 mg tablet or three-times-a-day dosing with the 500/125 mg tablet, in adults. No differences between the 875 mg bid and 500mg t.i.d dosing regimes are seen when comparing the amoxicillin T½, or C_max after normalisation for the different doses of amoxicillin administered. Similarly, no differences are seen for the clavulanate T½, C_max or AUC values after appropriate dose normalisation.

The time of dosing of co-amoxiclav relative to the start of a meal has no marked effects on the pharmacokinetics of amoxicillin in adults. In a study of the 875/125 mg tablet, the time of dosing relative to ingestion of a meal had a marked effect on the pharmacokinetics of clavulanate. For clavulanate AUC and C_max, the highest mean values and smallest inter-subject variabilities were achieved by administering co-amoxiclav at the start of a meal, compared to the fasting state or 30 or 150 minutes after the start of a meal.

The mean C_max, T_max, T½, and AUC values for amoxicillin and clavulanic acid are given below for an 800 mg/114 mg dose of co-amoxiclav that were administered to male subjects who fasted for at least 12 hours.

### Mean Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Drug Administration</th>
<th>Dose (mg)</th>
<th>C_max (mg/L)</th>
<th>T_max * (hours)</th>
<th>AUC_{0-∞} (mg.h/L)</th>
<th>T½ (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>800 mg</td>
<td>13.04</td>
<td>1.25</td>
<td>33.83</td>
<td>1.33</td>
</tr>
<tr>
<td>Clavulanic acid</td>
<td>114 mg</td>
<td>2.32</td>
<td>1.00</td>
<td>5.11</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* Median values

Amoxicillin serum concentrations achieved with co-amoxiclav are similar to those produced by the oral administration of equivalent doses of amoxicillin alone.

### Distribution

Following intravenous administration therapeutic concentrations of both amoxicillin and clavulanic acid may be detected in the tissues and interstitial fluid. Therapeutic concentrations of both drugs have been found in gall bladder, abdominal tissue, skin, fat, and muscle tissues; fluids found to have therapeutic levels include synovial and peritoneal fluids, bile and pus.

Neither amoxicillin nor clavulanic acid is highly protein bound, studies show that about 25% for clavulanic acid and 18% for amoxicillin of total plasma drug content is bound to protein. From animal studies there is no evidence to suggest that either component accumulates in any organ.

Amoxicillin, like most penicillins, can be detected in breast milk. There are no data available on the passage of clavulanic acid into breast milk.

Reproduction studies in animals have shown that both amoxicillin and clavulanic acid penetrate the placental barrier. However, no evidence of impaired fertility or harm to the foetus was detected.

### Elimination

As with other penicillins, the major route of elimination for amoxicillin is via the kidney, whereas for clavulanate elimination is by both non-renal and renal mechanisms. Approximately 60-70% of the amoxicillin and approximately 40-65% of the clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of a single 375 or 625 mg tablet.
Amoxicillin is also partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to 10-25% of the initial dose. Clavulanic acid is extensively metabolised in man to 2,5-dihydro-4-(2-hydroxyethyl)-5-oxo-1H-pyrrole-3-carboxylic acid and 1-amino-4-hydroxy-butan-2-one and eliminated in urine and faeces and as carbon dioxide in expired air.

5.3 PRECLINICAL SAFETY DATA
No further information of relevance

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
sucrose ester (E 473)
kaolin heavy
triethyl citrate (E 1505)
Carrageenan (E 407)
methacrylic acid ethylacrylate copolymer 1:1 dispersion
calcium phosphate (E 341)
glycerol monostearate (E471)
polysorbate 80 (E 433)

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 sachets
Do not pinch or squash the straws

6.5 NATURE AND CONTENTS OF CONTAINER
Each aluminium sachet contains a blue translucent polypropylene straw that is sealed on one side by a polypropylene cap and on the other side by a polyester/polyolefin controller.

Pack sizes:
Cartons containing 2, 10, 14, 20, or 5x18 drinking straws.
Not all pack sizes may be marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Used straws can be put in household waste.

7 MARKETING AUTHORISATION HOLDER
Grüenthal Ltd. Regus Lakeside House 1 Furzeground Way Stockley Park East Uxbridge UB11 1BD United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 21727/0019

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
09/05/2007

10 DATE OF REVISION OF THE TEXT
09/05/2007
1  NAME OF THE MEDICINAL PRODUCT  
Riclasip® 400/57 mg granules for oral suspension

2  QUALITATIVE AND QUANTITATIVE COMPOSITION  
Riclasip 400/57 mg granules for oral suspension:  
Each drinking straw with 817.2 mg granules for oral suspension contains 400 mg amoxicillin  
(present as amoxicillin trihydrate) and 57 mg clavulanic acid (present as potassium clavulanate)

For excipients, see section 6.1

3  PHARMACEUTICAL FORM  
Granules for oral suspension.

White to yellowish granules (amoxicillin) and yellowish to greyish granules (clavulanic acid).

4  CLINICAL PARTICULARS  
4.1 THERAPEUTIC INDICATIONS  
Riclasip granules for oral suspension is an antibiotic agent with a notably broad spectrum of  
activity against the commonly occurring bacterial pathogens in general practice and hospital.  
The β-lactamase inhibitory action of clavulanate extends the spectrum of amoxicillin to  
embrace a wider range of organisms, including many resistant to other β-lactam antibiotics.

Riclasip granules for oral suspension, for twice-daily (b.i.d) oral dosing, is indicated for short- 
term treatment of bacterial infections at the following sites when amoxicillin resistant β - 
lactamase-producing strains are suspected as the cause. In other situations, amoxicillin alone  
should be considered.
- **Upper Respiratory Tract Infections** (including ENT) in particular sinusitis, otitis media,  
  recurrent tonsillitis. These infections are often caused by *Streptococcus pneumoniae*,  
  *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pyogenes*.
- **Lower Respiratory Tract Infections** in particular acute exacerbations of chronic bronchitis  
  (especially if considered severe), bronchopneumonia. These infections are often caused by  
  *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*.
- **Urinary Tract Infections** in particular cystitis (especially when recurrent or complicated  
  - excluding prostatitis). These infections are often caused by *Enterobacteriaceae* (mainly  
  *Escherichia coli*), *Staphylococcus saprophyticus*, *Enterococcus species*.
- **Skin and Soft Tissue Infections** in particular cellulitis, animal bites and severe dental  
  abscess with spreading cellulitis. These infections are often caused by *Staphylococcus aureus*,  
  *Streptococcus pyogenes* and *Bacteroides species*.
- A comprehensive list of sensitive organisms is provided in Section 5.
  * Some members of these species of bacteria produce β-lactamase, rendering them insensitive  
  to amoxicillin alone.

Mixed infections caused by amoxicillin-susceptible organisms in conjunction with Riclasip  
granules for oral suspension -susceptible β-lactamase-producing organisms may be treated  
with Riclasip granules for oral suspension. These infections should not require the addition of  
another antibiotic resistant to β-lactamases.

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**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dosage</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 - 6 years (13 - 21 kg)</td>
<td>25/3.6 mg/kg/day</td>
<td>200/28.5 mg Riclasip granules for oral suspension b.i.d.</td>
</tr>
<tr>
<td>7 - 9 years (22 – 31 kg)</td>
<td>45/6.4 mg/kg/day</td>
<td>300/42.75 mg Riclasip granules for oral suspension b.i.d.</td>
</tr>
<tr>
<td>10 - 12 years (32 - 40 kg)</td>
<td>30/4.3 mg/kg/day</td>
<td>400/57 mg (or 2x 200/28.5 mg) Riclasip granules for oral suspension b.i.d.</td>
</tr>
</tbody>
</table>

Riclasip granules for oral suspension are not suitable for patients incapable of using an ordinary drinking straw (e.g. children younger than 2 years). These patients should use other forms of co-amoxiclav.

**Infants with immature kidney function**
For children with immature renal function Riclasip granules for oral suspension is not recommended.

**Renal impairment**
For patients with a GFR of >30 ml/min no adjustment in dosage is required. For patients with a GFR of ≤30 ml/min Riclasip granules for oral suspension 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.

**Riclasip granules for oral suspension should be used according to the instructions below.**

Riclasip granules for oral suspension straws are sealed in sachets for single-use. Immediately before use, the sachet is to be torn at the upper notch and pulled down. When handling the straw, damage by pinching and squashing must be avoided.
The straw is taken out of the sachet sideways keeping it upright (the cap should be at the top).

The cap is pulled upwards. The straw should not be turned upside-down. Care must be taken not to spill any of the contained granules.

The lower end of the straw containing a white “controller” is put into a suitable drink. Suitable drinks are clear fluids (hot beverages above 40 °C should be avoided) which are not viscous or containing solid particles, e.g. lemonades, fruit juices (without pulp), homogenised milk (up to 3.5% fat), tea or water. Carbonated drinks should be preferred as these can mask the sensation in the mouth caused by the granules. Full-fat milk (> 3.5% fat), milk-shakes or drinks with particles should not be used as they may clog the straw.

The drink is sipped through the straw. During sipping, the granules are dispersed. Riclasip granules for oral suspension straws contain a single dose of co-amoxiclav, all of which is to be taken at the same time. Several sips may be required to complete the dose. Biting the granules should be avoided. Chewing and biting on the straw should be avoided.

During sipping, the granules are dispersed and the white controller moves upwards, however, it remains in the straw. The controller is not part of the medication. Finally, an adequate amount of beverage should be drunk and remaining granules should be swallowed by flushing the mouth with the drink.

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Changes in liver function tests have been observed in some patients receiving co-amoxiclav. The clinical significance of these changes is uncertain but co-amoxiclav should be used with caution in patients with evidence of hepatic dysfunction.
Cholestatic jaundice, which may be severe, but is usually reversible, has been reported rarely. Signs and symptoms may not become apparent for several weeks after treatment has ceased.

In patients with mild renal impairment (GFR > 30 ml/min), no dosage adjustment is needed (see Section 4.2) In patients with moderate or severe renal impairment (GFR ≤ 30 ml/min) Riclasip granules for oral suspension is not recommended.

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria (see Section 4.9 Overdose).

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity (see Section 4.3).

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

Prolonged use may also occasionally result in overgrowth of non-susceptible organisms.

This medicinal product contains sucrose ester which might be a source of sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. The maximum amount of sucrose that might be formed out the sucrose ester is 3.5 – 7 mg per straw, depending on the strength.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Prolongation of bleeding time and prothrombin time have been reported in some patients receiving co-amoxiclav. Co-amoxiclav should be used with care in patients on anti-coagulation therapy. In common with other broad-spectrum antibiotics, co-amoxiclav may reduce the efficacy of oral contraceptives and patients should be warned accordingly.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. There are no data on the concomitant use of co-amoxiclav and allopurinol.

4.6 PREGNANCY AND LACTATION

Use in pregnancy

Reproduction studies in animals (mice and rats) with orally and parenterally administered co-amoxiclav have shown no teratogenic effects. In a single study in women with preterm, premature rupture of the foetal membrane (pPROM), it was reported that prophylactic treatment with co-amoxiclav may be associated with an increased risk of necrotising enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the physician.

Use in lactation

Co-amoxiclav may be administered during the period of lactation. With the exception of the risk of sensitisation, associated with the excretion of trace quantities in breast milk, there are no known detrimental effects for the breast-fed infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Adverse effects on the ability to drive or operate machinery have not been observed.

4.8 UNDESIRABLE EFFECTS

Side effects are uncommon and mainly of a mild and transitory nature.

Gastrointestinal reactions:
Diarrhoea, indigestion, nausea, vomiting, and mucocutaneous candidiasis have been reported. Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) has been reported rarely. Nausea, although uncommon, is more often associated with higher oral dosages. If gastrointestinal side effects occur with oral therapy they may be reduced by taking co-amoxiclav at the start of meals. Superficial tooth discolouration has been reported rarely, mostly with the suspension. It can usually be removed by brushing.

Renal and urinary tract disorders:
Crystalluria has been reported very rarely (see Section 4.9 Overdose).

Genito-urinary effects:
Vaginal itching, soreness and discharge may occur.

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

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

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

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

4.9 OVERDOSE
Overdosage:
Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. They may be treated symptomatically, with attention to the water/electrolyte balance. Co-amoxiclav may be removed from the circulation by haemodialysis.

Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see Section 4.4 Special warnings and special precautions for use)

Drug abuse and dependence:
Drug dependency, addiction and recreational abuse have not been reported as a problem with this compound.
5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Riclasip granules for oral suspension contain a combination of amoxicillin and clavulanic acid, co-amoxiclav.

Pharmacotherapeutic group: Amoxicillin and enzyme inhibitors.

ATC code: J01CR02

Microbiology

Amoxicillin is a semi-synthetic antibiotic with a broad spectrum of antibacterial activity against many Gram-positive and Gram-negative micro-organisms. Amoxicillin is, however, susceptible to degradation by β-lactamases and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a β-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of β-lactamase enzymes commonly found in micro-organisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid mediated beta-lactamases frequently responsible for transferred drug resistance. It is generally less effective against chromosomally-mediated type 1 β-lactamases.

The presence of clavulanic acid in Riclasip granules for oral suspension protects amoxicillin from degradation by β-lactamase enzymes and effectively extends the antibacterial spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other penicillins and cephalosporins. Thus Riclasip granules for oral suspension possesses the distinctive properties of a broad spectrum antibiotic and a β-lactamase inhibitor. Riclasip granules for oral suspension is bactericidal to a wide range of organisms including:

Gram-positive

Aerobes: Enterococcus faecalis*, Enterococcus faecium*, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus viridans, Staphylococcus aureus*, Coagulase negative staphylococci* (including Staphylococcus epidermidis*), Corynebacterium species, Bacillus anthracis*, Listeria monocytogenes.

Anaerobes: Clostridium species, Peptococcus species, Peptostreptococcus.

Gram-negative


Anaerobes: Bacteroides species* including B. fragilis.

* Some members of these species of bacteria produce β-lactamase, rendering them insensitive to amoxicillin alone.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

The two components of Riclasip granules for oral suspension, amoxicillin and clavulanic acid, are each fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption of co-amoxiclav is optimised when taken at the start of a meal.

Pharmacokinetics

Pharmacokinetic studies have been performed in children, including one study which has compared co-amoxiclav t.i.d and b.i.d. All of these data indicate that the elimination pharmacokinetics seen in adults also apply to children with mature kidney function.
The mean AUC values for amoxicillin are essentially the same following twice-a-day dosing with the 875/125 mg tablet or three-times-a-day dosing with the 500/125 mg tablet, in adults. No differences between the 875 mg bid and 500 mg t.i.d dosing regimes are seen when comparing the amoxicillin $T_{1/2}$ or $C_{\text{max}}$ after normalisation for the different doses of amoxicillin administered. Similarly, no differences are seen for the clavulanate $T_{1/2}$, $C_{\text{max}}$ or AUC values after appropriate dose normalisation.

The time of dosing of co-amoxiclav relative to the start of a meal has no marked effects on the pharmacokinetics of amoxicillin in adults. In a study of the 875/125 mg tablet, the time of dosing relative to ingestion of a meal had a marked effect on the pharmacokinetics of clavulanate. For clavulanate AUC and $C_{\text{max}}$, the highest mean values and smallest inter-subject variabilities were achieved by administering co-amoxiclav at the start of a meal, compared to the fasting state or 30 or 150 minutes after the start of a meal.

The mean $C_{\text{max}}$, $T_{\text{max}}$, $T_{1/2}$, and AUC values for amoxicillin and clavulanic acid are given below for an 800 mg/114 mg dose of co-amoxiclav that were administered to male subjects who fasted for at least 12 hours.

### Mean Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Drug Administration</th>
<th>Dose (mg)</th>
<th>$C_{\text{max}}$ (mg/L)</th>
<th>$T_{\text{max}}$ (hours)</th>
<th>$AUC_{0-\infty}$ (mg.h/L)</th>
<th>$T_{1/2}$ (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riclasip granules for oral suspension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>800</td>
<td>13.04</td>
<td>1.25</td>
<td>33.83</td>
<td>1.33</td>
</tr>
<tr>
<td>Clavulanic acid</td>
<td>114</td>
<td>2.32</td>
<td>1.00</td>
<td>5.11</td>
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</tr>
</tbody>
</table>

* Median values

Amoxicillin serum concentrations achieved with co-amoxiclav are similar to those produced by the oral administration of equivalent doses of amoxicillin alone.

**Distribution**

Following intravenous administration therapeutic concentrations of both amoxicillin and clavulanic acid may be detected in the tissues and interstitial fluid. Therapeutic concentrations of both drugs have been found in gall bladder, abdominal tissue, skin, fat, and muscle tissues; fluids found to have therapeutic levels include synovial and peritoneal fluids, bile and pus.

Neither amoxicillin nor clavulanic acid is highly protein bound, studies show that about 25% for clavulanic acid and 18% for amoxicillin of total plasma drug content is bound to protein. From animal studies there is no evidence to suggest that either component accumulates in any organ.

Amoxicillin, like most penicillins, can be detected in breast milk. There are no data available on the passage of clavulanic acid into breast milk.

Reproduction studies in animals have shown that both amoxicillin and clavulanic acid penetrate the placental barrier. However, no evidence of impaired fertility or harm to the foetus was detected.

**Elimination:**

As with other penicillins, the major route of elimination for amoxicillin is via the kidney, whereas for clavulanate elimination is by both non-renal and renal mechanisms. Approximately 60-70% of the amoxicillin and approximately 40-65% of the clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of a single 375 or 625 mg tablet.
Amoxicillin is also partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to 10-25% of the initial dose. Clavulanic acid is extensively metabolised in man to 2,5-dihydro-4-(2-hydroxyethyl)-5-oxo-1H-pyrrole-3-carboxylic acid and 1-amino-4-hydroxybutan-2-one and eliminated in urine and faeces and as carbon dioxide in expired air.

5.3 PRECLINICAL SAFETY DATA
No further information of relevance

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
sucrose ester (E 473)
kaolin heavy
triethyl citrate (E 1505)
Carrageenan (E 407)
methacrylic acid ethylacrylate copolymer 1:1 dispersion
calcium phosphate (E 341)
glycerol monostearate (E471)
polysorbate 80 (E 433)

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 sachets
Do not pinch or squash the straws

6.5 NATURE AND CONTENTS OF CONTAINER
Each aluminum sachet contains a blue translucent polypropylene straw that is sealed on one side by a polypropylene cap and on the other side by a polyester/polyolefin controller.

Pack sizes:
Cartons containing 2, 10, 14, 20, or 5x18 drinking straws.
Not all pack sizes may be marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Used straws can be put in household waste.

7 MARKETING AUTHORISATION HOLDER
Grüenthal Ltd.
Regus Lakeside House
1 Furzeground Way
Stockley Park East
Uxbridge UB11 1BD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 21727/0020

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
09/05/2007

10 DATE OF REVISION OF THE TEXT
09/05/2007
NAME OF THE MEDICINAL PRODUCT
Co-amoxiclav DST Grünenthal 200/28.5 mg granules for oral suspension

QUALITATIVE AND QUANTITATIVE COMPOSITION
Co-amoxiclav DST Grünenthal 200/28.5 mg granules for oral suspension:
Each drinking straw with 408.6 mg granules for oral suspension contains 200 mg amoxicillin (present as amoxicillin trihydrate) and 28.5 mg clavulanic acid (present as potassium clavulanate)

For excipients, see section 6.1

PHARMACEUTICAL FORM
Granules for oral suspension.

White to yellowish granules (amoxicillin) and yellowish to greyish granules (clavulanic acid).

CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS
Co-amoxiclav DST Grünenthal granules for oral suspension is an antibiotic agent with a notably broad spectrum of activity against the commonly occurring bacterial pathogens in general practice and hospital. The β-lactamase inhibitory action of clavulanate extends the spectrum of amoxicillin to embrace a wider range of organisms, including many resistant to other β-lactam antibiotics.

Co-amoxiclav DST Grünenthal granules for oral suspension, for twice-daily (b.i.d) oral dosing, is indicated for short-term treatment of bacterial infections at the following sites when amoxicillin resistant β-lactamase-producing strains are suspected as the cause. In other situations, amoxicillin alone should be considered.
- **Upper Respiratory Tract Infections (including ENT)** in particular sinusitis, otitis media, recurrent tonsillitis. These infections are often caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*.*, Moraxella catarrhalis* and *Streptococcus pyogenes*.
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- **Urinary Tract Infections** in particular cystitis (especially when recurrent or complicated - excluding prostatitis). These infections are often caused by *Enterobacteriaceae* (mainly *Escherichia coli*), *Staphylococcus saprophyticus*, *Enterococcus* species.*
- **Skin and Soft Tissue Infections** in particular cellulitis, animal bites and severe dental abscess with spreading cellulitis. These infections are often caused by *Staphylococcus aureus*, *Streptococcus pyogenes* and *Bacteroides* species*.
- A comprehensive list of sensitive organisms is provided in Section 5.
* Some members of these species of bacteria produce β-lactamase, rendering them insensitive to amoxicillin alone.

Mixed infections caused by amoxicillin-susceptible organisms in conjunction with co-amoxiclav DST Grünenthal granules for oral suspension -susceptible β-lactamase-producing organisms may be treated with co-amoxiclav DST Grünenthal granules for oral suspension. These infections should not require the addition of another antibiotic resistant to β-lactamases.

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**

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<th>25/3.6 mg/kg/day</th>
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Co-amoxiclav DST Grünenthal granules for oral suspension are not suitable for patients incapable of using an ordinary drinking straw (e.g. children younger than 2 years). These patients should use other forms of co-amoxiclav.

*Infants with immature kidney function*
For children with immature renal function co-amoxiclav DST Grünenthal granules for oral suspension is not recommended.

*Renal impairment*
For patients with a GFR of >30 ml/min no adjustment in dosage is required. For patients with a GFR of ≤30 ml/min co-amoxiclav DST Grünenthal granules for oral suspension 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.

Co-amoxiclav DST Grünenthal granules for oral suspension should be used according to the instructions below.
Co-amoxiclav DST Grünenthal granules for oral suspension straws are sealed in sachets for single-use. Immediately before use, the sachet is to be torn at the upper notch and pulled down. When handling the straw, damage by pinching and squashing must be avoided.

The straw is taken out of the sachet sideways keeping it upright (the cap should be at the top).

The cap is pulled upwards. The straw should not be turned upside-down. Care must be taken not to spill any of the contained granules.

The lower end of the straw containing a white “controller” is put into a suitable drink. Suitable drinks are clear fluids (hot beverages above 40 °C should be avoided) which are not viscous or containing solid particles, e.g. lemonades, fruit juices (without pulp), homogenised milk (up to 3.5% fat), tea or water. Carbonated drinks should be preferred as these can mask the sensation in the mouth caused by the granules. Full-fat milk (> 3.5% fat), milk-shakes or drinks with particles should not be used as they may clog the straw.

The drink is sipped through the straw. During sipping, the granules are dispersed. Co-amoxiclav DST Grünenthal granules for oral suspension straws contain a single dose of co-amoxiclav, all of which is to be taken at the same time. Several sips may be required to complete the dose. Biting the granules should be avoided. Chewing and biting on the straw should be avoided.

During sipping, the granules are dispersed and the white controller moves upwards, however, it remains in the straw. The controller is not part of the medication. Finally, an adequate amount of beverage should be drunk and remaining granules should be swallowed by flushing the mouth with the drink.

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Changes in liver function tests have been observed in some patients receiving co-amoxiclav. The clinical significance of these changes is uncertain but co-amoxiclav should be used with caution in patients with evidence of hepatic dysfunction.

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

In patients with mild renal impairment (GFR > 30 ml/min), no dosage adjustment is needed (see Section 4.2) In patients with moderate or severe renal impairment (GFR ≤ 30 ml/min) co-amoxiclav DST Grünenthal granules for oral suspension is not recommended.

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria (see Section 4.9 Overdose).

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity (see Section 4.3).

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

Prolonged use may also occasionally result in overgrowth of non-susceptible organisms.

This medicinal product contains sucrose ester which might be a source of sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. The maximum amount of sucrose that might be formed out the sucrose ester is 3.5 – 7 mg per straw, depending on the strength.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Prolongation of bleeding time and prothrombin time have been reported in some patients receiving co-amoxiclav. Co-amoxiclav should be used with care in patients on anti-coagulation therapy. In common with other broad-spectrum antibiotics, co-amoxiclav may reduce the efficacy of oral contraceptives and patients should be warned accordingly.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. There are no data on the concomitant use of co-amoxiclav and allopurinol.

4.6 PREGNANCY AND LACTATION
Use in pregnancy
Reproduction studies in animals (mice and rats) with orally and parenterally administered co-amoxiclav have shown no teratogenic effects. In a single study in women with preterm, premature rupture of the foetal membrane (pPROM), it was reported that prophylactic treatment with co-amoxiclav may be associated with an increased risk of necrotising enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the physician.

Use in lactation
Co-amoxiclav may be administered during the period of lactation. With the exception of the risk of sensitisation, associated with the excretion of trace quantities in breast milk, there are no known detrimental effects for the breast-fed infant.
4.7  **EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**
Adverse effects on the ability to drive or operate machinery have not been observed.

4.8  **UNDESIRABLE EFFECTS**
Side effects are uncommon and mainly of a mild and transitory nature.

  **Gastrointestinal reactions:**
  Diarrhoea, indigestion, nausea, vomiting, and mucocutaneous candidiasis have been reported. Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) has been reported rarely. Nausea, although uncommon, is more often associated with higher oral dosages. If gastrointestinal side effects occur with oral therapy they may be reduced by taking co-amoxiclav at the start of meals. Superficial tooth discolouration has been reported rarely, mostly with the suspension. It can usually be removed by brushing.

  **Renal and urinary tract disorders:**
  Crystalluria has been reported very rarely (see Section 4.9 Overdose).

  **Genito-urinary effects:**
  Vaginal itching, soreness and discharge may occur.

  **Hepatic effects:**
  Moderate and asymptomatic rises in AST and/or ALT and alkaline phosphatases have been reported occasionally. Hepatitis and cholestatic jaundice have been reported rarely. These hepatic reactions have been reported more commonly with co-amoxiclav than with other penicillins. After co-amoxiclav hepatic reactions have been reported more frequently in males and elderly patients, particularly those over 65 years. The risk increases with duration of treatment longer than 14 days. These reactions have been very rarely reported in children.

  Signs and symptoms usually occur during or shortly after treatment but in some cases may not occur until several weeks after treatment has ended. Hepatic reactions are usually reversible but they may be severe and, very rarely, deaths have been reported.

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

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

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

4.9  **OVERDOSE**

  **Overdosage:**
  Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. They may be treated symptomatically, with attention to the water/electrolyte balance. Co-amoxiclav may be removed from the circulation by haemodialysis.
Amoxicillin crystaluria, in some cases leading to renal failure, has been observed (see Section 4.4 Special warnings and special precautions for use)

Drug abuse and dependence:
Drug dependency, addiction and recreational abuse have not been reported as a problem with this compound.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Co-amoxiclav DST Grünenthal granules for oral suspension contains a combination of amoxicillin and clavulanic acid, co-amoxiclav.

Pharmacotherapeutic group: Amoxicillin and enzyme inhibitors.

ATC code: J01CR02

Microbiology:
Amoxicillin is a semi-synthetic antibiotic with a broad spectrum of antibacterial activity against many Gram-positive and Gram-negative micro-organisms. Amoxicillin is, however, susceptible to degradation by β-lactamases and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a β-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of β-lactamase enzymes commonly found in micro-organisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid mediated beta-lactamases frequently responsible for transferred drug resistance. It is generally less effective against chromosomally-mediated type 1 β-lactamases.

The presence of clavulanic acid in co-amoxiclav DST Grünenthal granules for oral suspension protects amoxicillin from degradation by β-lactamase enzymes and effectively extends the antibacterial spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other penicillins and cephalosporins. Thus co-amoxiclav DST Grünenthal granules for oral suspension possesses the distinctive properties of a broad spectrum antibiotic and a β-lactamase inhibitor. Co-amoxiclav DST Grünenthal granules for oral suspension is bactericidal to a wide range of organisms including:

Gram-positive
Aerobes: Enterococcus faecalis*, Enterococcus faecium*, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus viridans, Staphylococcus aureus*, Coagulase negative staphylococci* (including Staphylococcus epidermidis*), Corynebacterium species, Bacillus anthracis*, Listeria monocytogenes.
Anaerobes: Clostridium species, Peptococcus species, Peptostreptococcus.

Gram-negative
Anaerobes: Bacteroides species* including B. fragilis.

* Some members of these species of bacteria produce β-lactamase, rendering them insensitive to amoxicillin alone.

5.2 PHARMACOKINETIC PROPERTIES

Absorption
The two components of co-amoxiclav DST Grünenthal granules for oral suspension, amoxicillin and clavulanic acid, are each fully dissociated in aqueous solution at physiological
pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption of co-amoxiclav is optimised when taken at the start of a meal.

**Pharmacokinetics**

Pharmacokinetic studies have been performed in children, including one study which has compared co-amoxiclav t.i.d and b.i.d. All of these data indicate that the elimination pharmacokinetics seen in adults also apply to children with mature kidney function.

The mean AUC values for amoxicillin are essentially the same following twice-a-day dosing with the 875/125 mg tablet or three-times-a-day dosing with the 500/125 mg tablet, in adults. No differences between the 875 mg bid and 500mg t.i.d dosing regimes are seen when comparing the amoxicillin T½, or Cmax after normalisation for the different doses of amoxicillin administered. Similarly, no differences are seen for the clavulanate T½, Cmax or AUC values after appropriate dose normalisation.

The time of dosing of co-amoxiclav relative to the start of a meal has no marked effects on the pharmacokinetics of amoxicillin in adults. In a study of the 875/125 mg tablet, the time of dosing relative to ingestion of a meal had a marked effect on the pharmacokinetics of clavulanate. For clavulanate AUC and Cmax, the highest mean values and smallest inter-subject variabilities were achieved by administering co-amoxiclav at the start of a meal, compared to the fasting state or 30 or 150 minutes after the start of a meal.

The mean Cmax, Tmax, T½ and AUC values for amoxicillin and clavulanic acid are given below for an 800 mg/114 mg dose of co-amoxiclav that were administered to male subjects who fasted for at least 12 hours.

<table>
<thead>
<tr>
<th>Drug Administration</th>
<th>Dose (mg)</th>
<th>Cmax (mg/L)</th>
<th>Tmax (hours)</th>
<th>AUC0-∞ (mg.h/L)</th>
<th>T½ (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-amoxiclav DST Grünenthal granules for oral suspension</td>
<td>Amoxicillin</td>
<td>800</td>
<td>13.04</td>
<td>1.25</td>
<td>33.83</td>
</tr>
<tr>
<td></td>
<td>Clavulanic acid</td>
<td>114</td>
<td>2.32</td>
<td>1.00</td>
<td>5.11</td>
</tr>
</tbody>
</table>

* Median values

Amoxicillin serum concentrations achieved with co-amoxiclav are similar to those produced by the oral administration of equivalent doses of amoxicillin alone.

**Distribution**

Following intravenous administration therapeutic concentrations of both amoxicillin and clavulanic acid may be detected in the tissues and interstitial fluid. Therapeutic concentrations of both drugs have been found in gall bladder, abdominal tissue, skin, fat, and muscle tissues; fluids found to have therapeutic levels include synovial and peritoneal fluids, bile and pus.

Neither amoxicillin nor clavulanic acid is highly protein bound, studies show that about 25% for clavulanic acid and 18% for amoxicillin of total plasma drug content is bound to protein. From animal studies there is no evidence to suggest that either component accumulates in any organ.

Amoxicillin, like most penicillins, can be detected in breast milk. There are no data available on the passage of clavulanic acid into breast milk.

Reproduction studies in animals have shown that both amoxicillin and clavulanic acid penetrate the placental barrier. However, no evidence of impaired fertility or harm to the foetus was detected.
Elimination:
As with other penicillins, the major route of elimination for amoxicillin is via the kidney, whereas for clavulanate elimination is by both non-renal and renal mechanisms. Approximately 60-70% of the amoxicillin and approximately 40-65% of the clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of a single 375 or 625 mg tablet.

Amoxicillin is also partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to 10-25% of the initial dose. Clavulanic acid is extensively metabolised in man to 2,5-dihydro-4-(2-hydroxyethyl)-5-oxo-1H-pyrrole-3-carboxylic acid and 1-amino-4-hydroxy-butan-2-one and eliminated in urine and faeces and as carbon dioxide in expired air.

5.3 PRECLINICAL SAFETY DATA
No further information of relevance

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
sucrose ester (E 473)
kaolin heavy
triethyl citrate (E 1505)
Carrageenan (E 407)
methacrylic acid ethylacrylate copolymer 1:1 dispersion
calcium phosphate (E 341)
glycerol monostearate (E471)
polysorbate 80 (E 433)

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 sachets
Do not pinch or squash the straws

6.5 NATURE AND CONTENTS OF CONTAINER
Each aluminium sachet contains a blue translucent polypropylene straw that is sealed on one side by a polypropylene cap and on the other side by a polyester/polyolefin controller.

Pack sizes:
Cartons containing 2, 10, 14, 20, or 5x18 drinking straws.
Not all pack sizes may be marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Used straws can be put in household waste.

7 MARKETING AUTHORISATION HOLDER
Grüenthal Ltd.
Regus Lakeside House
1 Furzeground Way
Stockley Park East
Uxbridge UB11 1BD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 21727/0021
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION 09/05/2007

10 DATE OF REVISION OF THE TEXT 09/05/2007
1 NAME OF THE MEDICINAL PRODUCT
Co-amoxiclav DST Grünenthal 300/42.75 mg granules for oral suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Co-amoxiclav DST Grünenthal 300/42.75 mg granules for oral suspension:
Each drinking straw with 613 mg granules for oral suspension contains 300 mg amoxicillin (present as amoxicillin trihydrate) and 42.75 mg clavulanic acid (present as potassium clavulanate).

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Granules for oral suspension.

White to yellowish granules (amoxicillin) and yellowish to greyish granules (clavulanic acid).

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS
Co-amoxiclav DST Grünenthal granules for oral suspension is an antibiotic agent with a notably broad spectrum of activity against the commonly occurring bacterial pathogens in general practice and hospital. The β-lactamase inhibitory action of clavulanate extends the spectrum of amoxicillin to embrace a wider range of organisms, including many resistant to other β-lactam antibiotics.

Co-amoxiclav DST Grünenthal granules for oral suspension, for twice-daily (b.i.d) oral dosing, is indicated for short-term treatment of bacterial infections at the following sites when amoxicillin resistant β-lactamase-producing strains are suspected as the cause. In other situations, amoxicillin alone should be considered.
- **Upper Respiratory Tract Infections (including ENT)** in particular sinusitis, otitis media, recurrent tonsillitis. These infections are often caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* *, Moraxella catarrhalis* *, and *Streptococcus pyogenes*.
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- **Urinary Tract Infections** in particular cystitis (especially when recurrent or complicated - excluding prostatitis). These infections are often caused by *Enterobacteriaceae* * (mainly *Escherichia coli* *), Staphylococcus saprophyticus*, *Enterococcus species* *
- **Skin and Soft Tissue Infections** in particular cellulitis, animal bites and severe dental abscess with spreading cellulitis. These infections are often caused by *Staphylococcus aureus*, *Streptococcus pyogenes* and *Bacteroides* * species* *
- A comprehensive list of sensitive organisms is provided in Section 5.
* Some members of these species of bacteria produce β-lactamase, rendering them insensitive to amoxicillin alone.

Mixed infections caused by amoxicillin-susceptible organisms in conjunction with co-amoxiclav DST Grünenthal granules for oral suspension -susceptible β-lactamase-producing organisms may be treated with co-amoxiclav DST Grünenthal granules for oral suspension. These infections should not require the addition of another antibiotic resistant to β-lactamases.

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**

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Co-amoxiclav DST Grünenthal granules for oral suspension are not suitable for patients incapable of using an ordinary drinking straw (e.g. children younger than 2 years). These patients should use other forms of co-amoxiclav.

**Infants with immature kidney function**

For children with immature renal function co-amoxiclav DST Grünenthal granules for oral suspension is not recommended.

**Renal impairment**

For patients with a GFR of >30 ml/min no adjustment in dosage is required. For patients with a GFR of ≤30 ml/min co-amoxiclav DST Grünenthal granules for oral suspension 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.

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The cap is pulled upwards. The straw should not be turned upside-down. Care must be taken not to spill any of the contained granules.

The lower end of the straw containing a white “controller” is put into a suitable drink. Suitable drinks are clear fluids (hot beverages above 40 °C should be avoided) which are not viscous or containing solid particles, e.g. lemonades, fruit juices (without pulp), homogenised milk (up to 3.5% fat), tea or water. Carbonated drinks should be preferred as these can mask the sensation in the mouth caused by the granules. Full-fat milk (> 3.5% fat), milk-shakes or drinks with particles should not be used as they may clog the straw.

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During sipping, the granules are dispersed and the white controller moves upwards, however, it remains in the straw. The controller is not part of the medication. Finally, an adequate amount of beverage should be drunk and remaining granules should be swallowed by flushing the mouth with the drink.

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Penicillin hypersensitivity.
Attention should be paid to possible cross-sensitivity with other β-lactam antibiotics, e.g. cephalosporins.
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In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria (see Section 4.9 Overdose).

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity (see Section 4.3).

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

Prolonged use may also occasionally result in overgrowth of non-susceptible organisms.

This medicinal product contains sucrose ester which might be a source of sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. The maximum amount of sucrose that might be formed out of the sucrose ester is 3.5 – 7 mg per straw, depending on the strength.

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Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. There are no data on the concomitant use of co-amoxiclav and allopurinol.

4.6 PREGNANCY AND LACTATION
Use in pregnancy
Reproduction studies in animals (mice and rats) with orally and parenterally administered co-amoxiclav have shown no teratogenic effects. In a single study in women with preterm, premature rupture of the foetal membrane (pPROM), it was reported that prophylactic treatment with co-amoxiclav may be associated with an increased risk of necrotising enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the physician.

Use in lactation
Co-amoxiclav may be administered during the period of lactation. With the exception of the risk of sensitisation, associated with the excretion of trace quantities in breast milk, there are no known detrimental effects for the breast-fed infant.
4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Adverse effects on the ability to drive or operate machinery have not been observed.

4.8 UNDESIRABLE EFFECTS
Side effects are uncommon and mainly of a mild and transitory nature.

Gastrointestinal reactions:
Diarrrhoea, indigestion, nausea, vomiting, and mucocutaneous candidiasis have been reported. Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) has been reported rarely. Nausea, although uncommon, is more often associated with higher oral dosages. If gastrointestinal side effects occur with oral therapy they may be reduced by taking co-amoxiclav at the start of meals. Superficial tooth discolouration has been reported rarely, mostly with the suspension. It can usually be removed by brushing.

Renal and urinary tract disorders:
Crystalluria has been reported very rarely (see Section 4.9 Overdose).

Genito-urinary effects:
Vaginal itching, soreness and discharge may occur.

Hepatic effects:
Moderate and asymptomatic rises in AST and/or ALT and alkaline phosphatases have been reported occasionally. Hepatitis and cholestatic jaundice have been reported rarely. These hepatic reactions have been reported more commonly with co-amoxiclav than with other penicillins. After co-amoxiclav hepatic reactions have been reported more frequently in males and elderly patients, particularly those over 65 years. The risk increases with duration of treatment longer than 14 days. These reactions have been very rarely reported in children.

Signs and symptoms usually occur during or shortly after treatment but in some cases may not occur until several weeks after treatment has ended. Hepatic reactions are usually reversible but they may be severe and, very rarely, deaths have been reported.

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

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

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

4.9 OVERDOSE
Overdosage:
Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. They may be treated symptomatically, with attention to the water/electrolyte balance. Co-amoxiclav may be removed from the circulation by haemodialysis.
Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see Section 4.4 Special warnings and special precautions for use)

**Drug abuse and dependence:**
Drug dependency, addiction and recreational abuse have not been reported as a problem with this compound.

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **PHARMACODYNAMIC PROPERTIES**

Co-amoxiclav DST Grünenthal granules for oral suspension contains a combination of amoxicillin and clavulanic acid, co-amoxiclav.

Pharmacotherapeutic group: Amoxicillin and enzyme inhibitors.

ATC code: J01CR02

**Microbiology**
Amoxicillin is a semi-synthetic antibiotic with a broad spectrum of antibacterial activity against many Gram-positive and Gram-negative micro-organisms. Amoxicillin is, however, susceptible to degradation by β-lactamases and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a β-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of β-lactamase enzymes commonly found in micro-organisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid mediated beta-lactamases frequently responsible for transferred drug resistance. It is generally less effective against chromosomally-mediated type 1 β-lactamases.

The presence of clavulanic acid in co-amoxiclav DST Grünenthal granules for oral suspension protects amoxicillin from degradation by β-lactamase enzymes and effectively extends the antibacterial spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other penicillins and cephalosporins. Thus co-amoxiclav DST Grünenthal granules for oral suspension possesses the distinctive properties of a broad spectrum antibiotic and a β-lactamase inhibitor. Co-amoxiclav DST Grünenthal granules for oral suspension is bactericidal to a wide range of organisms including:

**Gram-positive**
Aerobes: *Enterococcus faecalis*, *Enterococcus faecium*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus viridans*, *Staphylococcus aureus*, *Coagulase negative staphylococci* (including *Staphylococcus epidermidis*), *Corynebacterium species*, *Bacillus anthracis*, *Listeria monocytogenes*.
Anaerobes: *Clostridium species*, *Peptococcus species*, *Peptostreptococcus*.

**Gram-negative**
Anaerobes: *Bacteroides species* including *B. fragilis*.

* Some members of these species of bacteria produce β-lactamase, rendering them insensitive to amoxicillin alone.

5.2 **PHARMACOKINETIC PROPERTIES**

**Absorption**
The two components of co-amoxiclav DST Grünenthal granules for oral suspension, amoxicillin and clavulanic acid, are each fully dissociated in aqueous solution at physiological
pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption of co-amoxiclav is optimised when taken at the start of a meal.

Pharmacokinetics
Pharmacokinetic studies have been performed in children, including one study which has compared co-amoxiclav t.i.d and b.i.d. All of these data indicate that the elimination pharmacokinetics seen in adults also apply to children with mature kidney function.

The mean AUC values for amoxicillin are essentially the same following twice-a-day dosing with the 875/125 mg tablet or three-times-a-day dosing with the 500/125 mg tablet, in adults. No differences between the 875 mg bid and 500mg t.i.d dosing regimes are seen when comparing the amoxicillin T½, or Cmax after normalisation for the different doses of amoxicillin administered. Similarly, no differences are seen for the clavulanate T½, Cmax or AUC values after appropriate dose normalisation.

The time of dosing of co-amoxiclav relative to the start of a meal has no marked effects on the pharmacokinetics of amoxicillin in adults. In a study of the 875/125 mg tablet, the time of dosing relative to ingestion of a meal had a marked effect on the pharmacokinetics of clavulanate. For clavulanate AUC and Cmax, the highest mean values and smallest inter-subject variabilities were achieved by administering co-amoxiclav at the start of a meal, compared to the fasting state or 30 or 150 minutes after the start of a meal.

The mean Cmax, Tmax, T½ and AUC values for amoxicillin and clavulanic acid are given below for an 800 mg/114 mg dose of co-amoxiclav that were administered to male subjects who fasted for at least 12 hours.

<table>
<thead>
<tr>
<th>Drug Administration</th>
<th>Dose</th>
<th>Cmax</th>
<th>Tmax</th>
<th>AUC 0-∞</th>
<th>T½</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-amoxiclav DST</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grunenthal granules for oral suspension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>800 mg</td>
<td>13.04</td>
<td>1.25</td>
<td>33.83</td>
<td>1.33</td>
</tr>
<tr>
<td>Clavulanic acid</td>
<td>114 mg</td>
<td>2.32</td>
<td>1.00</td>
<td>5.11</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* Median values

Amoxicillin serum concentrations achieved with co-amoxiclav are similar to those produced by the oral administration of equivalent doses of amoxicillin alone.

Distribution
Following intravenous administration therapeutic concentrations of both amoxicillin and clavulanic acid may be detected in the tissues and interstitial fluid. Therapeutic concentrations of both drugs have been found in gall bladder, abdominal tissue, skin, fat, and muscle tissues; fluids found to have therapeutic levels include synovial and peritoneal fluids, bile and pus.

Neither amoxicillin nor clavulanic acid is highly protein bound, studies show that about 25% for clavulanic acid and 18% for amoxicillin of total plasma drug content is bound to protein. From animal studies there is no evidence to suggest that either component accumulates in any organ.

Amoxicillin, like most penicillins, can be detected in breast milk. There are no data available on the passage of clavulanic acid into breast milk.

Reproduction studies in animals have shown that both amoxicillin and clavulanic acid penetrate the placental barrier. However, no evidence of impaired fertility or harm to the foetus was detected.
Elimination:
As with other penicillins, the major route of elimination for amoxicillin is via the kidney, whereas for clavulanate elimination is by both non-renal and renal mechanisms. Approximately 60-70% of the amoxicillin and approximately 40-65% of the clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of a single 375 or 625 mg tablet.

Amoxicillin is also partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to 10-25% of the initial dose. Clavulanic acid is extensively metabolised in man to 2,5-dihydro-4-(2-hydroxyethyl)-5-oxo-1H-pyrrole-3-carboxylic acid and 1-amino-4-hydroxybutan-2-one and eliminated in urine and faeces and as carbon dioxide in expired air.

5.3 PRECLINICAL SAFETY DATA
No further information of relevance

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
sucrose ester (E 473)
kaolin heavy
triethyl citrate (E 1505)
Carrageenan (E 407)
methacrylic acid ethylacrylate copolymer 1:1 dispersion
calcium phosphate (E 341)
glycerol monostearate (E471)
polysorbate 80 (E 433)

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 sachets
Do not pinch or squash the straws

6.5 NATURE AND CONTENTS OF CONTAINER
Each aluminium sachet contains a blue translucent polypropylene straw that is sealed on one side by a polypropylene cap and on the other side by a polyester/polyolefin controller.

Pack sizes:
Cartons containing 2, 10, 14, 20, or 5x18 drinking straws.
Not all pack sizes may be marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Used straws can be put in household waste.

7 MARKETING AUTHORISATION HOLDER
Grüenthal Ltd.
Regus Lakeside House
1 Furzeground Way
Stockley Park East
Uxbridge UB11 1BD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 21727/0022
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
09/05/2007

10 DATE OF REVISION OF THE TEXT
09/05/2007
1 NAME OF THE MEDICINAL PRODUCT
Co-amoxiclav DST Grünenthal 400/57 mg granules for oral suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Co-amoxiclav DST Grünenthal 400/57 mg granules for oral suspension:
Each drinking straw with 817.2 mg granules for oral suspension contains 400 mg amoxicillin (present as amoxicillin trihydrate) and 57 mg clavulanic acid (present as potassium clavulanate)

For excipients, see section 6.1

3 PHARMACEUTICAL FORM
Granules for oral suspension.

White to yellowish granules (amoxicillin) and yellowish to greyish granules (clavulanic acid).

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS
Co-amoxiclav DST Grünenthal granules for oral suspension is an antibiotic agent with a notably broad spectrum of activity against the commonly occurring bacterial pathogens in general practice and hospital. The β-lactamase inhibitory action of clavulanate extends the spectrum of amoxicillin to embrace a wider range of organisms, including many resistant to other β-lactam antibiotics.

Co-amoxiclav DST Grünenthal granules for oral suspension, for twice-daily (b.i.d) oral dosing, is indicated for short-term treatment of bacterial infections at the following sites when amoxicillin resistant β-lactamase-producing strains are suspected as the cause. In other situations, amoxicillin alone should be considered.
- Upper Respiratory Tract Infections (including ENT) in particular sinusitis, otitis media, recurrent tonsillitis. These infections are often caused by Streptococcus pneumoniae, Haemophilus influenzae*, Moraxella catarrhalis* and Streptococcus pyogenes.
- Lower Respiratory Tract Infections in particular acute exacerbations of chronic bronchitis (especially if considered severe), bronchopneumonia. These infections are often caused by Streptococcus pneumoniae, Haemophilus influenzae* and Moraxella catarrhalis*.
- Urinary Tract Infections in particular cystitis (especially when recurrent or complicated - excluding prostatis). These infections are often caused by Enterobacteriaceae* (mainly Escherichia coli*), Staphylococcus saprophyticus, Enterococcus species.*
- Skin and Soft Tissue Infections in particular cellulitis, animal bites and severe dental abscess with spreading cellulitis. These infections are often caused by Staphylococcus aureus*, Streptococcus pyogenes and Bacteroides species*.
- A comprehensive list of sensitive organisms is provided in Section 5.
* Some members of these species of bacteria produce β-lactamase, rendering them insensitive to amoxicillin alone.

Mixed infections caused by amoxicillin-susceptible organisms in conjunction with co-amoxiclav DST Grünenthal granules for oral suspension -susceptible β-lactamase-producing organisms may be treated with co-amoxiclav DST Grünenthal granules for oral suspension. These infections should not require the addition of another antibiotic resistant to β-lactamases.

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

<table>
<thead>
<tr>
<th>Dose</th>
<th>Age</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>25/3.6  mg/kg/day</td>
<td>2 - 6 years (13 - 21 kg)</td>
<td>200/28.5 mg co-amoxiclav DST Grünenthal granules for oral suspension b.i.d.</td>
</tr>
<tr>
<td></td>
<td>7 - 9 years (22 – 31 kg)</td>
<td>300/42.75 mg co-amoxiclav DST Grünenthal granules for oral suspension b.i.d.</td>
</tr>
<tr>
<td></td>
<td>10 - 12 years (32 - 40 kg)</td>
<td>400/57 mg (or 2x 200/28.5 mg) co-amoxiclav DST Grünenthal granules for oral suspension b.i.d.</td>
</tr>
<tr>
<td>45/6.4  mg/kg/day</td>
<td>2 - 6 years (13 - 21 kg)</td>
<td>400/57 mg (or 2x 200/28.5 mg) co-amoxiclav DST Grünenthal granules for oral suspension b.i.d.</td>
</tr>
<tr>
<td></td>
<td>7 - 9 years (22 – 31 kg)</td>
<td>2x 300/42.75 mg co-amoxiclav DST Grünenthal granules for oral suspension b.i.d.</td>
</tr>
<tr>
<td></td>
<td>10 - 12 years (32 - 40 kg)</td>
<td>2x 400/57 mg co-amoxiclav DST Grünenthal granules for oral suspension b.i.d.</td>
</tr>
</tbody>
</table>

Co-amoxiclav DST Grünenthal granules for oral suspension are not suitable for patients incapable of using an ordinary drinking straw (e.g. children younger than 2 years). These patients should use other forms of co-amoxiclav.

Infants with immature kidney function
For children with immature renal function co-amoxiclav DST Grünenthal granules for oral suspension is not recommended.

Renal impairment
For patients with a GFR of >30 ml/min no adjustment in dosage is required. For patients with a GFR of ≤30 ml/min co-amoxiclav DST Grünenthal granules for oral suspension 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.

Co-amoxiclav DST Grünenthal granules for oral suspension should be used according to the instructions below.
Co-amoxiclav DST Grünenthal granules for oral suspension straws are sealed in sachets for single-use. Immediately before use, the sachet is to be torn at the upper notch and pulled down. When handling the straw, damage by pinching and squashing must be avoided.

The straw is taken out of the sachet sideways keeping it upright (the cap should be at the top).

The cap is pulled upwards. The straw should not be turned upside-down. Care must be taken not to spill any of the contained granules.

The lower end of the straw containing a white “controller” is put into a suitable drink. Suitable drinks are clear fluids (hot beverages above 40 °C should be avoided) which are not viscous or containing solid particles, e.g. lemonades, fruit juices (without pulp), homogenised milk (up to 3.5% fat), tea or water. Carbonated drinks should be preferred as these can mask the sensation in the mouth caused by the granules. Full-fat milk (>3.5% fat), milk-shakes or drinks with particles should not be used as they may clog the straw.

The drink is sipped through the straw. During sipping, the granules are dispersed. Co-amoxiclav DST Grünenthal granules for oral suspension straws contain a single dose of co-amoxiclav, all of which is to be taken at the same time. Several sips may be required to complete the dose. Biting the granules should be avoided. Chewing and biting on the straw should be avoided.

During sipping, the granules are dispersed and the white controller moves upwards, however, it remains in the straw. The controller is not part of the medication. Finally, an adequate amount of beverage should be drunk and remaining granules should be swallowed by flushing the mouth with the drink.

4.3 CONTRAINDICATIONS
Penicillin hypersensitivity.
Attention should be paid to possible cross-sensitivity with other β-lactam antibiotics, e.g. cephalosporins.

A previous history of co-amoxiclav- or penicillin-associated jaundice/hepatic dysfunction should be noted.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

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

In patients with mild renal impairment (GFR > 30 ml/min), no dosage adjustment is needed (see Section 4.2). In patients with moderate or severe renal impairment (GFR ≤ 30 ml/min) co-amoxiclav DST Grünenthal granules for oral suspension is not recommended.

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria (see Section 4.9 Overdose).

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity (see Section 4.3).

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

Prolonged use may also occasionally result in overgrowth of non-susceptible organisms.

This medicinal product contains sucrose ester which might be a source of sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. The maximum amount of sucrose that might be formed out the sucrose ester is 3.5 – 7 mg per straw, depending on the strength.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Prolongation of bleeding time and prothrombin time have been reported in some patients receiving co-amoxiclav. Co-amoxiclav should be used with care in patients on anticoagulation therapy. In common with other broad-spectrum antibiotics, co-amoxiclav may reduce the efficacy of oral contraceptives and patients should be warned accordingly.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. There are no data on the concomitant use of co-amoxiclav and allopurinol.

4.6 PREGNANCY AND LACTATION

Use in pregnancy

Reproduction studies in animals (mice and rats) with orally and parenterally administered co-amoxiclav have shown no teratogenic effects. In a single study in women with preterm, premature rupture of the foetal membrane (pPROM), it was reported that prophylactic treatment with co-amoxiclav may be associated with an increased risk of necrotising enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the physician.

Use in lactation

Co-amoxiclav may be administered during the period of lactation. With the exception of the risk of sensitisation, associated with the excretion of trace quantities in breast milk, there are no known detrimental effects for the breast-fed infant.
4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Adverse effects on the ability to drive or operate machinery have not been observed.

4.8 UNDESIRABLE EFFECTS
Side effects are uncommon and mainly of a mild and transitory nature.

Gastrointestinal reactions:
Diarrhoea, indigestion, nausea, vomiting, and mucocutaneous candidiasis have been reported. Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) has been reported rarely. Nausea, although uncommon, is more often associated with higher oral dosages. If gastrointestinal side effects occur with oral therapy they may be reduced by taking co-amoxiclav at the start of meals. Superficial tooth discolouration has been reported rarely, mostly with the suspension. It can usually be removed by brushing.

Renal and urinary tract disorders:
Crystalluria has been reported very rarely (see Section 4.9 Overdose).

Genito-urinary effects:
Vaginal itching, soreness and discharge may occur.

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

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

4.9 OVERDOSE
Overdosage:
Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. They may be treated symptomatically, with attention to the water/electrolyte balance. Co-amoxiclav may be removed from the circulation by haemodialysis.
Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see Section 4.4 Special warnings and special precautions for use)

**Drug abuse and dependence:**
Drug dependency, addiction and recreational abuse have not been reported as a problem with this compound.

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The presence of clavulanic acid in co-amoxiclav DST Grünenthal granules for oral suspension protects amoxicillin from degradation by β-lactamase enzymes and effectively extends the antibacterial spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other penicillins and cephalosporins. Thus co-amoxiclav DST Grünenthal granules for oral suspension possesses the distinctive properties of a broad spectrum antibiotic and a β-lactamase inhibitor. Co-amoxiclav DST Grünenthal granules for oral suspension is bactericidal to a wide range of organisms including:

**Gram-positive**
Aerobes: *Enterococcus faecalis*, *Enterococcus faecium*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus viridans*, *Staphylococcus aureus*, *Coagulase negative staphylococci* (including *Staphylococcus epidermidis*), *Corynebacterium species*, *Bacillus anthracis*, *Listeria monocytogenes*.
Anaerobes: *Clostridium species*, *Peptococcus species*, *Peptostreptococcus*.

**Gram-negative**
Anaerobes: *Bacteroides species* including *B. fragilis*.

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The two components of co-amoxiclav DST Grünenthal granules for oral suspension, amoxicillin and clavulanic acid, are each fully dissociated in aqueous solution at physiological
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Pharmacokinetics
Pharmacokinetic studies have been performed in children, including one study which has compared co-amoxiclav t.i.d and b.i.d. All of these data indicate that the elimination pharmacokinetics seen in adults also apply to children with mature kidney function.

The mean AUC values for amoxicillin are essentially the same following twice-a-day dosing with the 875/125 mg tablet or three-times-a-day dosing with the 500/125 mg tablet, in adults. No differences between the 875 mg bid and 500mg t.i.d dosing regimes are seen when comparing the amoxicillin T½, or Cmax after normalisation for the different doses of amoxicillin administered. Similarly, no differences are seen for the clavulanate T½, Cmax or AUC values after appropriate dose normalisation.

The time of dosing of co-amoxiclav relative to the start of a meal has no marked effects on the pharmacokinetics of amoxicillin in adults. In a study of the 875/125 mg tablet, the time of dosing relative to ingestion of a meal had a marked effect on the pharmacokinetics of clavulanate. For clavulanate AUC and Cmax, the highest mean values and smallest inter-subject variabilities were achieved by administering co-amoxiclav at the start of a meal, compared to the fasting state or 30 or 150 minutes after the start of a meal.

The mean Cmax, Tmax, T½ and AUC values for amoxicillin and clavulanic acid are given below for an 800 mg/114 mg dose of co-amoxiclav that were administered to male subjects who fasted for at least 12 hours.

### Mean Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Drug Administration</th>
<th>Dose</th>
<th>Cmax</th>
<th>Tmax *</th>
<th>AUC0-∞</th>
<th>T½</th>
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<tr>
<td>Co-amoxiclav DST</td>
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<td>for oral suspension</td>
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<td>Amoxicillin</td>
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<td>13.04</td>
<td>1.25</td>
<td>33.83</td>
<td>1.33</td>
</tr>
<tr>
<td>Clavulanic acid</td>
<td>114mg</td>
<td>2.32</td>
<td>1.00</td>
<td>5.11</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* Median values

Amoxicillin serum concentrations achieved with co-amoxiclav are similar to those produced by the oral administration of equivalent doses of amoxicillin alone.

### Distribution

Following intravenous administration therapeutic concentrations of both amoxicillin and clavulanic acid may be detected in the tissues and interstitial fluid. Therapeutic concentrations of both drugs have been found in gall bladder, abdominal tissue, skin, fat, and muscle tissues; fluids found to have therapeutic levels include synovial and peritoneal fluids, bile and pus.

Neither amoxicillin nor clavulanic acid is highly protein bound, studies show that about 25% for clavulanic acid and 18% for amoxicillin of total plasma drug content is bound to protein. From animal studies there is no evidence to suggest that either component accumulates in any organ.

Amoxicillin, like most penicillins, can be detected in breast milk. There are no data available on the passage of clavulanic acid into breast milk.

Reproduction studies in animals have shown that both amoxicillin and clavulanic acid penetrate the placental barrier. However, no evidence of impaired fertility or harm to the foetus was detected.
Elimination:
As with other penicillins, the major route of elimination for amoxicillin is via the kidney, whereas for clavulanate elimination is by both non-renal and renal mechanisms. Approximately 60-70% of the amoxicillin and approximately 40-65% of the clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of a single 375 or 625 mg tablet.

Amoxicillin is also partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to 10-25% of the initial dose. Clavulanic acid is extensively metabolised in man to 2,5-dihydro-4-(2-hydroxyethyl)-5-oxo-1H-pyrrole-3-carboxylic acid and 1-amino-4-hydroxy-butan-2-one and eliminated in urine and faeces and as carbon dioxide in expired air.

5.3 PRECLINICAL SAFETY DATA
No further information of relevance

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
sucrose ester (E 473)
kaolin heavy
triethyl citrate (E 1505)
Carrageenan (E 407)
methacrylic acid ethylacrylate copolymer 1:1 dispersion
calcium phosphate (E 341)
glycerol monostearate (E471)
polysorbate 80 (E 433)

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 sachets
Do not pinch or squash the straws

6.5 NATURE AND CONTENTS OF CONTAINER
Each aluminium sachet contains a blue translucent polypropylene straw that is sealed on one side by a polypropylene cap and on the other side by a polyester/polyolefin controller.

Pack sizes:
Cartons containing 2, 10, 14, 20, or 5x18 drinking straws.
Not all pack sizes may be marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Used straws can be put in household waste.

7 MARKETING AUTHORISATION HOLDER
Grüenthal Ltd.
Regus Lakeside House
1 Furzeground Way
Stockley Park East
Uxbridge UB11 1BD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 21727/0023
Rilcasip® 200/28.5 mg granules for oral suspension
Rilcasip® 300/42.75 mg granules for oral suspension
Rilcasip® 400/57 mg granules for oral suspension

Amoxicillin/Clavulanic acid

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

Keep this leaflet. You may need to read it again.

If you have any further questions, please ask your doctor or your pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

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

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

1. WHAT RILCASIP IS AND WHAT IT IS USED FOR

Rilcasip is an antibiotic for treating infections. It belongs to a group of antibiotics called "penicillins.

Rilcasip works by killing the bacteria that cause infections. The antibiotic in Rilcasip 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 (abcesses).

2. BEFORE YOU USE RILCASIP

Do not use Rilcasip:
- Do not use Rilcasip if you have:
  - ever had a skin rash or swelling of the face or neck when taking an antibiotic.
  - an allergy to penicillins (or any other antibiotic).
  - ever had a serious complaint – such as liver problems – when taking an antibiotic.

In these instances, do not use and consult your doctor for advice on alternative medicines.

Take special care with Rilcasip:
- If your child has glandular fever or
- if your child is receiving treatment for:
  - liver or kidney problems
  - prevention of blood clots (e.g. warfarin)
  - gout or a similar condition caused by uric acid build up (e.g. allopurinol)
  - if your doctor may decide to give your child a different medicine or change the dose of Rilcasip.

Take other medicines:
- Please tell your doctor or pharmacist if your child is taking or has recently taken any other medicine including medicines obtained without a prescription.

Using Rilcasip with food and drink
- Please notice section 3, paragraph "How to use the Rilcasip drinking straw" (see 4) which informs which kind of drinks can be used for taking Rilcasip granules for oral suspension.

Pregnancy and breast-feeding
- If you are female and know or suspect that you are pregnant, you always should speak to your doctor before using Rilcasip.

Driving and using machines
- There are no studies about an effect of Rilcasip on the ability to drive or use machines.

When performing these activities the possible occurrence of the adverse reactions e.g. dizziness and convulsions should be taken into account.

Important information about some of the ingredients of Rilcasip
- This medicine contains sucrose ester, a possible source of sucrose. If your doctor has informed you that you (or your child) do not tolerate certain sugars, contact your doctor before taking this medicine.

3. HOW TO USE RILCASIP

Always take care that Rilcasip is used exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

Rilcasip is not suitable for children under 2 years of age and for patients unable to use an ordinary drinking straw.

The dose that your doctor tells you to take will depend on the type of infection your child has and the age or weight of your child. The usual doses are shown in the table below. Each single dose should be taken twice daily, for instance in the morning and in the evening.

For the best results, your child should use Rilcasip just before meals.

Try to give this medicine as part of the daily routine for example at the start of a meal, once in the morning and once in the evening. But remember, when ever you give your child the medicine, space the doses as evenly as possible through the day.

Try not to give your child more than one single dose every 12 hours and never give two single doses within about four hours of each other.

Never give more than the recommended dose each day.

It’s now much easier to give medicines to children thanks to the new medicine-containing drinking straw. It will help you to give your child the right dose while sipping a drink of his or her choice.

How to use the Rilcasip drinking straw:
- Take a sachet containing a straw from the Rilcasip carton. Immediately before use, open the sachet by tearing it at the upper notch and pulling down. Do not pinch or squeeze the straw.
- Take the straw sideways out of the sachet keeping it upright (the cap should be at the top).
- Pull the cap upwards. Do not turn the straw upside-down in order not to spill the granules with the active substance.
- Put the lower end of the straw (closed by a white “controller” preventing granules from leaving the straw at the bottom) into a cup or glass with a drink of your choice.
- Have your child sip the drink through the straw. Your child should not bite or chew on the straw in order to ensure correct functioning of the straw. Your child should take the whole dose of the straw at the same time. Several sips may be required to complete the dose. Your child should swallow the dispersed granules directly and avoid chewing them.
- When the drink is being sipped through the straw, the white "controller" rises, but stays in the straw. The controller may not always move up to the very end of the straw or may come down again after use. The white "controller" is not part of the medication.
- Finally, drink an adequate amount and swallow any granules remaining in your mouth by flushing with the drink.
UKPAR Riclesiap/Co-amoxiclav DST Grunenthal 200/28.5mg, 300/42.75mg, 400/57mg Granules for Oral Suspension
PL 21727/0018-23

4. POSSIBLE SIDE EFFECTS

Unlike all medicines, Riclesiap can cause side effects, although not everybody gets them.

If you notice any of the serious side effects mentioned or you (or your child) develop any unexpected or unusual symptoms, please inform your doctor or pharmacist.

See your doctor straight away in case you notice one of the following situations with your child:
- severe diarrhoea with vomiting;
- urination is becoming darker or faeces becoming paler;
- the skin or the whites of your child's eyes turning yellow;
- it starts to itch or gets a rash;
- getting a swollen face or breathing problems.

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

Other side effects that can occur with Riclesiap are:

Uncommon:
- less than 1 in 100, but more than 1 in 1,000 persons treated
- diarrhoea, upset stomach, feeling sick.
- if this happens, the symptoms are usually mild and you may prevent them by giving your child suck dose just before meals.
- Thrush (a yeast infection of the mouth, vagina or skin folds causing itching and soreness). You can get treatments for thrush from your doctor or pharmacist.

Rare:
- less than 1 in 1,000, but more than 1 in 10,000 persons treated
- slight yellow/brown staining of the teeth.
- Such staining usually disappears shortly after treatment if teeth are brushed regularly.
- Increase in bleeding time

Very rare:
- less than 1 in 10,000 persons treated and isolated cases
- Hyperactivity, dizziness, headache and convulsions.
- These symptoms are reversible.
- Crystals in the urine (usually only visible under a microscope) which may be characterised by cloudy urine or by difficulty/discomfort in passing urine.

Remind your doctor if your child is having blood tests, because Riclesiap sometimes causes short-term changes in blood cell counts.

5. HOW TO STORE RICLESIAP

- Do not store above 25°C.
- Medicines should not be disposed of via the wastewater or via the household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Riclesiap contains

The active substances are amoxicillin and clavulanic acid which are together also known as co-amoxiclav.

Riclesiap 200/28.5 mg granules for oral suspension:
- Each drinking straw with granules for oral suspension contains 200 mg amoxicillin and 28.5 mg clavulanic acid.
- Riclesiap 300/42.75 mg granules for oral suspension:
- Each drinking straw with granules for oral suspension contains 300 mg amoxicillin and 42.75 mg clavulanic acid.
- Riclesiap 400/57 mg granules for oral suspension:
- Each drinking straw with granules for oral suspension contains 400 mg amoxicillin and 57 mg clavulanic acid.

The other ingredients in Riclesiap granules for oral suspension are sucrose (E 427), aspartame (E 951), sodium saccharin (E 950), polyethylene glycol 400 (E 433), methacrylic acid ethylhexyl acrylate copolymer 1:1 dispersion, calcium phosphate (E 341), glycerol monostearate (E 471) and polyethylene 80 (E 433).

What Riclesiap looks like and contents of the pack

Riclesiap granules for oral suspension consists of white to yellowish and grey granules which are to be taken by mouth. The granules are contained in a blue translucent drinking straw which allows to take the granules as a suspension while sipping a drink.

Your child's Riclesiap comes in packs containing 2, 19, 14, 20, or 5x18 drinking straws. Not all pack sizes may be marketed.

Marketing Authorisation Holder and

Grunenthal GmbH
Ragus Lakeside House, 1 Fuzzarground Way
Shoreham Park East, Uxbridge
Middlesex UB11 1BD
United Kingdom

Manufacturer

Grunenthal GmbH
Zöglerstraße 6
52078 Aachen
Germany

This leaflet was last approved in (MM/YYYY).
Riclesiap is a registered trademark of Grunenthal GmbH.
UKPAR Ricitasp/Co-amoxiclav DST Grünenthal 200/28.5mg, 300/42.75mg, 400/57mg Granules for Oral Suspension

PL 21727/0018-23

PACKAGE LEAFLET: INFORMATION FOR THE USER

c-co-amoxiclav DST Grünenthal 200/28.5 mg granules for oral suspension
c-co-amoxiclav DST Grünenthal 300/42.75 mg granules for oral suspension
c-co-amoxiclav DST Grünenthal 400/57 mg granules for oral suspension

Amoxicillin/Clavulanic acid

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

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

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

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

Co-amoxiclav DST Grünenthal is an antibiotic for treating infections. It belongs to a group of antibiotics called "penicillins".

Co-amoxiclav DST Grünenthal works by killing the bacteria that can cause infections.

Co-amoxiclav DST Grünenthal 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 (abcesses).

2. BEFORE YOU USE CO-AMOXICLAV DST GRÜNENTHAL

Do not use co-amoxiclav DST Grünenthal:
Do not use co-amoxiclav DST Grünenthal if your child has:

• ever had a skin rash or swelling of the face or neck when taking an antibiotic,
• an allergy to penicillin or any other antibiotic,
• ever had a serious complaint – such as liver problems – when taking an antibiotic.

In these instances, do not use and consult your doctor for advice on alternative medicines.

Take special care with co-amoxiclav DST Grünenthal:

• If your child has granulomatous liver or
• if your child is receiving treatment for:
  • liver or kidney problems
  • prevention of blood clotting (e.g. warfarin)
  • gout or a similar condition caused by uric acid build up (e.g. allopurinol)

If so, your doctor may decide to give your child a different medicine or change the dose of co-amoxiclav DST Grünenthal.

Taking other medicines
Please tell your doctor or pharmacist if your child is taking or has recently taken any other medicine including medicines obtained without a prescription.

Using co-amoxiclav DST Grünenthal with food and drink
Please notice section 3, paragraph “How to use the co-amoxiclav DST Grünenthal drinking straw” (step 4) which informs which kind of drinks can be used for taking co-amoxiclav DST Grünenthal granules for oral suspension.

Pregnancy and breast-feeding

If you are female and know or suspect that you are pregnant, you always should speak to your doctor before using co-amoxiclav DST Grünenthal.

Driving and using machines

There are no studies about an effect of co-amoxiclav DST Grünenthal on the ability to drive or use machines. When performing these activities the possible occurrence of the adverse reactions e.g. dizziness and convulsions should be taken into account.

Important information about some of the ingredients of co-amoxiclav DST Grünenthal

This medicine contains sucrose ester, a possible source of sucrose. If your doctor has informed you that you (or your child) do not tolerate certain sugars, contact your doctor before taking this medicine.

3. HOW TO USE CO-AMOXICLAV DST GRÜNENTHAL

Always take care that co-amoxiclav DST Grünenthal is used exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

Co-amoxiclav DST Grünenthal is not suitable for children under 2 years of age and for patients unable to use an ordinary drinking straw.

The dose that your doctor tells you to take will depend on the type of infection your child has and the age or weight of your child. The usual doses are shown in the table below. Each single dose should be taken twice daily, for instance in the morning and in the evening.

<table>
<thead>
<tr>
<th>Age of child or Body weight</th>
<th>Mild to moderate infection</th>
<th>Severe infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to 6 years (13 to 21 kg)</td>
<td>1 straw co-amoxiclav DST Grünenthal 200/28.5 mg twice a day</td>
<td>1 straw co-amoxiclav DST Grünenthal 400/57 mg or 2 straws co-amoxiclav DST Grünenthal 200/28.5 mg twice a day</td>
</tr>
<tr>
<td>7 to 9 years (22 to 31 kg)</td>
<td>1 straw co-amoxiclav DST Grünenthal 300/42.75 mg twice a day</td>
<td>2 straws co-amoxiclav DST Grünenthal 400/57 mg twice a day</td>
</tr>
<tr>
<td>10 to 12 years (32 to 40 kg)</td>
<td>1 straw co-amoxiclav DST Grünenthal 400/57 mg or 2 straws co-amoxiclav DST Grünenthal 200/28.5 mg twice a day</td>
<td></td>
</tr>
</tbody>
</table>

For the best results, your child should use co-amoxiclav DST Grünenthal just before meals.

Try to give this medicine as part of the daily routine for example at the start of a meal, once in the morning and once in the evening.

But remember, whenever you give your child the medicine, space the doses as evenly as possible through the day.

Try not to give your child more than one single dose every 12 hours and never give two single doses within about four hours of each other.

Never give more than the recommended dose each day.

It's now much easier to give medicines to children thanks to the new medicine-containing drinking straw. It will help you to give your child the right dose while skipping a drink of his or her choice.

How to use the co-amoxiclav DST Grünenthal drinking straw:

• Take a sachet containing a straw from the co-amoxiclav DST Grünenthal carton. Immediately before use, open the sachet by tearing it at the upper notch and pulling down. Do not pinch or squeeze the straw.

• Take the straw sideways out of the sachet keeping it upright (the cap should be at the top).

• Pull the cap upwards. Do not turn the straw upside-down in order not to spill the granules with the active substance.

• Put the lower end of the straw (closed by a white "controller" preventing granules from leaving the straw at the bottom) into a cup or glass with a drink of your choice.

• Have your child sip the drink through the straw. Your child should not bite or chew on the straw in order to assure correct functioning of the straw. Your child should take the whole dose of the straw at the same time. Several sips may be required to complete the dose. Your child should swallow the dispersed granules directly and avoid chewing them.
When the drink is being sipped through the straw, the white “controller” rises, but stays in the straw. The controller may not always move up to the very end of the straw or may come down again after use. The white “controller” is not part of the medication. Finally, drink an adequate amount and swallow any granules remaining in your mouth by flushing with the drink.

Which drinks can be used with co-amoxiclav DST Grünenthal?

Many drinks can be used, e.g. lemonade, fruit juice without pulp, cold or lukewarm tea, homogenised milk (up to 3.5% fat) or water. Carbonated drinks (e.g. Sparkling water, Lemonade, any kind of Fruit Juice) (clear juice without pulp) are preferable, as these mask the sensation of granules in the mouth. Avoid hot drinks (above 40 °C). Do not use beverages with particles, with fruit pulp, full-fat milk or milk shakes as these may clog the straw.

How long is the treatment?

Your doctor will tell you how long co-amoxiclav DST Grünenthal should be used. Do not stop treatment on your own decision, e.g. because your child feels better. If the use is stopped too early, the infection may return. If you have the impression that the effect of co-amoxiclav DST Grünenthal is too strong or too weak, talk to your doctor or pharmacist. You should not give your child this product beyond two weeks without seeing your doctor again first.

If you use more co-amoxiclav DST Grünenthal than you should

If you accidentally have given your child too many co-amoxiclav DST Grünenthal doses (overdose) or you suspect that your child has taken extra medicine, contact your doctor or local hospital casualty department at once. Show the doctor the medicine box or sachet.

If you forget to use co-amoxiclav DST Grünenthal

If you forget to give a dose don’t worry – just give it as soon as you remember. 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.

If you stop using co-amoxiclav DST Grünenthal

Do not stop the treatment on your own, for instance, if your child feels better. If you stop giving your child this medicine before the end of the course, some bacteria may survive and cause the infection to come back. If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, co-amoxiclav DST Grünenthal can cause side effects, although not everybody gets them.

If you notice any of the serious side effects mentioned or if you (or your child) develop any other unexpected or unusual symptoms, please inform your doctor or pharmacist.

See your doctor straight away if you notice one of the following situations with your child:

- severe diarrhoea with bleeding;
- urine is becoming darker or foaming becoming paler; or
- the skin or the whites of your child’s eyes turning yellow.
- it starts to itch or gets a rash
- getting a swollen face or breathing problems

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

Other side effects that can occur with co-amoxiclav DST Grünenthal are:

Uncommon: less than 1 in 100, but more than 1 in 1,000 persons treated

- Diarrhoea, upset stomach, feeling sick. If this happens, the symptoms are usually mild and you may prevent them by giving your child each dose just before meals.
- Thrush (a yeast infection of the mouth, vagina or skin folds causing itching and soreness). You can get treatments for thrush from your doctor or pharmacist.

Rare: less than 1 in 1,000, but more than 1 in 10,000 persons treated

- Slight yellow/brown staining of the teeth. Such discolouring usually disappears shortly after treatment if teeth are brushed regularly.
- Increase in bleeding time

Very rare: less than 1 in 10,000 persons treated and isolated cases

- Hypersensitivity, dizziness, headache and convulsions. These symptoms are reversible.
- Crystals in the urine (usually only visible under a microscope) which may be characterised by cloudy urine or by difficulty/discomfort in passing urine.

Remind your doctor if your child is having blood tests, because co-amoxiclav DST Grünenthal sometimes causes short-term changes in blood counts.

5. HOW TO STORE CO-AMOXICLAV DST GRÜNENTHAL

Keep out of the reach and sight of children.

Store co-amoxiclav DST Grünenthal in the original unopened sachet. Do not pinch or squish the straws within the sachet. Do not use co-amoxiclav DST Grünenthal after the expiry date which is stated on the sachet after "EXP:"

The expiry date refers to the last day of that month.

Do not store above 25°C.

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

6. FURTHER INFORMATION

What co-amoxiclav DST Grünenthal contains

The active substances are amoxicillin and clavulanic acid which are together also known as co-amoxiclav.

co-amoxiclav DST Grünenthal 200/28.5 mg granules for oral suspension:

Each drinking straw with granules for oral suspension contains 200 mg amoxicillin and 28.5 mg clavulanic acid.

co-amoxiclav DST Grünenthal 300/42.75 mg granules for oral suspension:

Each drinking straw with granules for oral suspension contains 300 mg amoxicillin and 42.75 mg clavulanic acid.

co-amoxiclav DST Grünenthal 400/57 mg granules for oral suspension:

Each drinking straw with granules for oral suspension contains 400 mg amoxicillin and 57 mg clavulanic acid.

The other ingredients in co-amoxiclav DST Grünenthal granules for oral suspension are: sucrose water (E 445), calcium carbonate (E 160), Carrageenan (E 407), methylcellulose (E 467), gelatin (E 441), sodium metabisulphite (E 223) and sorbitol (E 420).

What co-amoxiclav DST Grünenthal looks like and contents of the pack

Co-amoxiclav DST Granules for oral suspension consists of white to yellowish and grey granules which are to be taken by mouth. The granules are contained in a blue translucent drinking straw which allows to take the granules as a suspension while sipping a drink.

Your child’s co-amoxiclav DST Grünenthal comes in cartons containing 2, 10, 14, 29, or 50 drinking straws. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Grünenthal Limited

Regus Lakeside House, 1 Fuzeground Way Stockley Park East, Uxbridge Middlesex UB11 1BD United Kingdom

Manufacturer

Grünenthal GmbH

Ziegelstraße 6

32052 Aschen Germany

This leaflet was last approved in (MM/YYYY).
Co-amoxiclav DST Grünenthal is a registered trademark of Grünenthal GmbH

R-05-30706-01 SK817
LABELLING

Please note that representative packaging for each strength is provided only. Packaging for duplicates is not included, but is consistent with the packaging presented.
Ricasip 200/28.5 mg Granules for oral suspension
Amoxicillin/Clavulanic acid

Granules for oral suspension
One drinking straw contains:
200 mg amoxicillin (as amoxicillin trihydrate)
and 28.5 mg clavulanic acid (as potassium clavulanate).
For oral use.
10 drinking straws

Ricasip 200/28.5 mg Granules for oral suspension

Precautions to be noted before use.
Consultations on use.

UKPAR Ricasip/Co-amoxiclav DST Grunenthal 200/28.5mg, 300/42.75mg, 400/57mg Granules
for Oral Suspension

PL 21727/0018-23
UKPAR Riclasip/Co-amoxiclav DST Grunenthal 200/28.5mg, 300/42.75mg, 400/57mg Granules for Oral Suspension

PL 21727/0018-23

5 x 18 drinking straws

Riclasip® 200/28.5 mg
Granules for oral suspension

Amoxicillin/Clavulanic acid

Grüenthal Limited, Regus Lakeside House, 1 Furzeground Way, Stockley Park East, Uxbridge, Middlesex, UB 11 1BD United Kingdom
Riclasip® 300/42.75 mg
Granules for oral suspension
Amoxicillin/Clavulanic acid

Granules for oral suspension
One drinking straw contains:
300 mg amoxicillin (as amoxicillin trihydrate)
and 42.75 mg clavulanic acid (as potassium clavulanate)
For oral use.
10 drinking straws

Medicinal product subject to medical prescription.
Use as directed by your doctor.

Keep out of reach of children.
Store in an unopened bottle.
Do not store above 30°C.
Do not refrigerate the bottle (unopened).

This product contains a cross-water which might be a possible source of systemic pain. If this occurs:
Read the package leaflet before use.
Follow the detailed instructions in the package leaflet.

Marketing Authorisation Holder:
Grunenthal Ltd, Regis Lakeside House, 1 Farleigh Road, Stockley Park West, Uxbridge, Middlesex, UB11 1QD, United Kingdom
Riclasip® 300/42.75 mg Granules for oral suspension

Amoxicillin/Clavulanic acid

Grüenthal Limited, Regus Lakeside House, 1 Furzeground Way, Stockley Park East, Uxbridge, Middlesex, UB 11 1BD United Kingdom
Riclasp® 400/57 mg Granules for oral suspension
Amoxicillin/Clavulanic acid

Granules for oral suspension
One drinking straw contains:
400 mg amoxicillin (as amoxicillin trihydrate)
and 57 mg clavulanic acid (as potassium clavulanate).
For oral use.
14 drinking straws

Medicinal product subject to medical prescription. See also directions by your doctor. Keep out of the reach and sight of children. Store in the original packages. Do not store above 25°C. Do not freeze or expose the product within the package.

This product contains sucrose-water which might be a possible source of sucrose (see 4.8.2 section).

Read the package leaflet before use. Instructions on use.

14 drinking straws

Marketing Authorisation Holder:
GRUNENTHAL LIMITED, Pegus Lakeside House, 1 Purley Green Way, Shirley Park East, Uxbridge, Middlesex, UB8 1JG United Kingdom

PL 21727/0018-23
### Ricasip® 400/57 mg Granules for oral suspension

<table>
<thead>
<tr>
<th>Strength</th>
<th>Dosage Form</th>
<th>Pack Size</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>400/57 mg</td>
<td>Granules</td>
<td>30 x 1 g</td>
<td>Grunenthal Limited</td>
</tr>
</tbody>
</table>

**Amoxicillin/Clavulanic acid**

Grunenthal Limited, Regus Lakeside House, 1 Furzeground Way, Stockley Park East, Uxbridge, Middlesex, UB 11 1BD United Kingdom

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5 x 18 drinking straws

Ricasip® 400/57 mg Granules for oral suspension