

Clamoxyl Duo Forte 875/125

Clamoxyl Duo 500/125

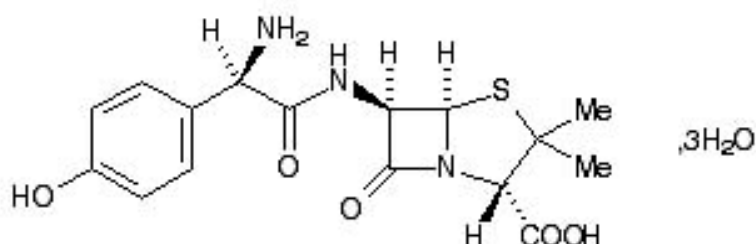


Amoxicillin Trihydrate and Potassium Clavulanate

PRODUCT INFORMATION

NAME OF THE MEDICINE

CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) and CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) tablets are combination products containing the semisynthetic antibiotic, amoxicillin (as the trihydrate) and the β -lactamase inhibitor clavulanic acid (as the potassium salt). The chemical name of amoxicillin is D-(-)- α -amino-p-hydroxybenzylpenicillin. It is susceptible to hydrolysis by β -lactamases. Amoxicillin trihydrate is represented structurally as:



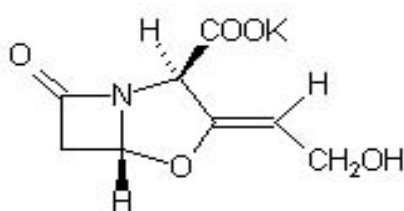
Molecular Formula: $C_{16}H_{19}N_3O_5S \cdot 3H_2O$

Molecular Weight: 419.5

CAS Registry No.: 61336-70-7

Clavulanic acid is produced by the fermentation of *Streptomyces clavuligerus*. It is an irreversible inhibitor of many β -lactamase enzymes except type 1 (Richmond). It is a β -lactam compound with only weak antibacterial activity.

The chemical name of potassium clavulanate is potassium Z-(2R,5R)-3-(β -hydroxyethylidene) clavam-2-carboxylate, and is represented structurally as:



Molecular Formula: $C_8H_8KNO_5$

Molecular Weight: 237.3

CAS Registry No.: 61177-45-5.

DESCRIPTION

Each CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) tablet contains 875 mg amoxicillin (an aminopenicillin) as the trihydrate, and 125 mg clavulanic acid as the potassium salt. CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) also contains the inactive ingredients: magnesium stearate, sodium starch glycolate, colloidal anhydrous silica and microcrystalline cellulose. The tablet coating contains titanium dioxide, hypromellose, Macrogol 4000 and Macrogol 6000.

Each CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablet contains 500 mg amoxicillin (an aminopenicillin) as the trihydrate, and 125 mg clavulanic acid as the potassium salt. CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablets also contain the inactive ingredients: magnesium stearate, sodium starch glycolate, colloidal anhydrous silica and –microcrystalline cellulose. The tablet coating contains titanium dioxide, hypromellose 5cps, hypromellose 15cps, Macrogol 4000, Macrogol 6000 and dimethicone 500.

PHARMACOLOGY

Pharmacokinetics

Amoxicillin is stable in the presence of gastric acid. The two components are rapidly absorbed if administered before or with a meal, but if given after meals, the serum levels of clavulanic acid are significantly reduced. To optimise absorption of clavulanic acid amoxicillin and clavulanic acid tablets should be administered at the start of a meal. The pharmacokinetics of amoxicillin are not affected by food.

Oral administration of amoxicillin and clavulanic acid (875mg/125 mg) tablets every 12 hours was compared with amoxicillin and clavulanic acid (500mg/125 mg) tablets every 8 hours at the start of a light meal. The following mean pharmacokinetic parameters were observed for amoxicillin for amoxicillin and clavulanic acid (875/125 mg) tablets taken every 12 hours and amoxicillin and clavulanic acid (500mg/125 mg) tablets taken every 8 hours respectively: peak plasma concentration (C_{max}) of 11.64 and 7.19 $\mu\text{g/mL}$, area under the plasma concentration-time curve between 0 and 24 hours after the first dose ($AUC_{(0-24 \text{ hours})}$) of 53.52 and 53.35 $\mu\text{g.h/mL}$, half life ($t_{1/2}$) of 1.19 and 1.15 hours, time to peak plasma concentration (T_{max}) of 1.50 and 1.50 hours and the time above the minimum inhibitory concentration (T_{MIC} 24 hours) of 10.46 hours and 13.30 hours.

The following pharmacokinetic parameters were observed for clavulanic acid for amoxicillin and clavulanic acid (875/125 mg) tablets taken every 12 hours and amoxicillin and clavulanic acid (500mg/125 mg) tablets taken every 8 hours respectively: C_{max} of 2.18 and 2.40 $\mu\text{g/mL}$, $AUC_{(0-24 \text{ hours})}$ of 10.16 and 15.72 $\mu\text{g.h/mL}$, $t_{1/2}$ of 0.96 and 0.98 hours and T_{max} of 1.25 and 1.50 hours, and (T_{MIC} 24 hours) of 6.08 hours and 9.43 hours.

The $t_{1/2}$ and C_{max} for clavulanate for amoxicillin and clavulanic acid (875/125 mg) tablets were not significantly different from amoxicillin and clavulanic acid (500/125 mg) tablets. However, the $AUC_{(0-24 \text{ hours})}$ was reduced, as would be expected with the lower daily dose of clavulanate (i.e. 250 mg in amoxicillin and clavulanic acid (875/125 mg) tablets vs 375 mg in amoxicillin and clavulanic acid (500/125 mg) tablets).

Oral administration of amoxicillin and clavulanic acid (500/125 mg) tablets every 12 hours was compared with amoxicillin and clavulanic acid (250mg/125 mg) tablets every 8 hours at the start of a light meal.

The following mean pharmacokinetic parameters were observed for amoxicillin for amoxicillin and clavulanic acid (500/125 mg) tablets taken every 12 hours and amoxicillin and clavulanic acid (250 mg/125 mg) tablets taken every 8 hours respectively: peak plasma concentration (C_{max}) of 6.51 and 3.32 $\mu\text{g/mL}$, area under the plasma concentration-time curve between 0 and 24 hours after the first dose ($AUC_{(0-24 \text{ hours})}$) of 33.43 and 26.66 $\mu\text{g.h/mL}$, half life ($t_{1/2}$) of 1.26 and 1.36 hours, time to peak plasma concentration (T_{max}) of 1.50 and 1.50 hours and the time above the minimum inhibitory concentration (T_{MIC} 24 hours) of 8.54 hours and 9.49 hours.

The following pharmacokinetic parameters were observed for clavulanic acid for amoxicillin and clavulanic acid (500/125 mg) tablets taken every 12 hours and amoxicillin and clavulanic acid (250 mg/125 mg) tablets taken every 8 hours respectively: C_{max} of 1.75 and 1.47 $\mu\text{g/mL}$, $AUC_{(0-24 \text{ hours})}$ of 8.6 and 12.6 $\mu\text{g.h/mL}$, $t_{1/2}$ of 1.01 and 1.01 hours and T_{max} of 1.50 and 1.50 hours, and (T_{MIC} 24 hours) of 5.69 hours and 8.24 hours.

Distribution: Following oral administration, both amoxicillin and clavulanic acid have been shown to diffuse in significant concentrations into pus, bile, and pleural, synovial and peritoneal fluids. Both penetrate

poorly into the CSF when the meninges are normal. Amoxicillin penetrates into the CSF better through inflamed meninges, but the maximum concentrations are still much lower than the peak serum levels. There are no data at present on the CSF penetration of clavulanic acid in patients with meningeal inflammation.

Neither amoxicillin nor clavulanic acid is highly protein bound. Clavulanic acid has been variously reported to be bound to human serum in the range of 9 - 30% and amoxicillin approximately 20% bound. From animal studies, there is no evidence to suggest either component accumulates in any organ.

Metabolism and Excretion: As with other penicillins, renal excretion is the major route of amoxicillin clearance, while clavulanate elimination is via both renal and non-renal mechanisms. Approximately 70% of the dose of amoxicillin is excreted in urine as amoxicillin. For clavulanic acid, following the administration of 125 mg of radiolabelled potassium clavulanate orally to normal volunteers 68% of the administered radioactivity was recovered in the urine in 24 hours. Of this 34% (ie. 23% of the administered dose) represented unchanged clavulanic acid.

2,5-dihydro-4-(2-hydroxyethyl)-5-oxo-1H-pyrrole-3-carboxylic acid (the major metabolite) and 1-amino-4-hydroxy-butan-2-one accounted for a further 23% and 12% (ie. 16% and 8% respectively of the administered dose). Small amounts of other yet unidentified metabolites were also present. These metabolites were also present in the urine of rat and dog. The extent of urinary excretion of clavulanic acid and its metabolites is lower in rat urine than in dog and human urine.

Concurrent administration of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid.

Microbiology

Like other penicillins, amoxicillin has a bactericidal effect on sensitive organisms during the stage of active multiplication. However, amoxicillin is susceptible to hydrolysis by β -lactamases and the addition of clavulanic acid in CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) or CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablets extends the antimicrobial spectrum of amoxicillin to include organisms normally resistant to amoxicillin due to β -lactamase production. *In vitro* studies have demonstrated the susceptibility of most strains of the following organisms:

Table 1 – Acquired resistance data for amoxicillin/clavulanic acid in Australia according to NCCLS guidelines (M100-S10) for amoxicillin/clavulanic acid

| | Number of Pathogens (n) | Percentage of Strains | |
|-----------------------------------|-------------------------|-----------------------|-----------|
| | | Intermediate | Resistant |
| <i>Streptococcus pneumoniae</i> * | 1020 | 0.3 | 0.1 |
| <i>Haemophilus influenzae</i> # | 303 | 0.0 | 0.3 |

*: - Data collected between March to November 1997.

#: - Data collected in 1999.

Table 2 – MIC Distribution for Sensitive/intermediate *S. pneumoniae* Isolates

| MIC \leq 1 | MIC $>1 < 2$ | MIC ≥ 2 |
|--------------|--------------|--------------|
| 96.8% | 2.3% | 0.9% |

Table 3 – Acquired resistance data for amoxicillin/clavulanic acid from other countries

| Breakpoints | Number of Pathogens (n) | Percentage acquired resistance (%) |
|---|-------------------------|------------------------------------|
| Sensitive aerobe gram positive | | |
| <i>Enterococcus faecalis</i> | 178 | 1.7 |
| <i>Enterococcus faecalis</i> | 178 | 1.7 |
| <i>Staphylococcus aureus</i> | 955 | 2 |
| <i>Staphylococcus aureus</i> (MSSA) | 2,458 | 2 |
| <i>Coagulase negative staphylococci</i> | 158 | 7 |

| | | |
|--|-------|------|
| <i>Streptococcus agalactiae</i> | 96 | 1 |
| <i>Streptococcus pneumoniae</i> | 196 | 8.5 |
| <i>Streptococcus pneumoniae</i> (Pen-S) | 154 | 0 |
| <i>Streptococcus pyogenes</i> | 76 | 0 |
| <i>Streptococcus species</i> | 28 | 0 |
| Sensitive aerobe gram negative | | |
| <i>Escherichia coli</i> | 946 | 5 |
| <i>Haemophilus influenzae</i> | 180 | 1.1 |
| <i>Haemophilus influenzae</i> (BLN) | 150 | 1.3 |
| <i>Haemophilus influenzae</i> (BLP) | 30 | 0 |
| <i>Klebsiella pneumoniae</i> | 355 | 1 |
| <i>Klebsiella oxytoca</i> | 1,540 | 9.6 |
| <i>Moraxella catarrhalis</i> | 46 | 0 |
| <i>Proteus sp.</i> | 128 | 5 |
| Sensitive anaerobe | | |
| <i>Clostridium species</i> | 42 | 0 |
| <i>Clostridium difficile</i> | 27 | 0 |
| <i>Peptostreptococcus species</i> | 17 | 0 |
| <i>Bacteroides fragilis</i> | 98 | 5 |
| <i>Bacteroides fragilis group</i> | 163 | 7 |
| <i>Fusobacterium species</i> | 16 | 0 |
| Intermediate aerobe gram negative | | |
| <i>Acinetobacter sp.</i> | 49 | 12 |
| Resistant aerobe gram positive | | |
| <i>Staphylococcus aureus</i> (MRSA) | 147 | 59.2 |
| Resistant aerobe gram negative | | |
| <i>Citrobacter sp.</i> | 84 | 56 |
| <i>Enterobacter sp.</i> | 181 | 86 |
| <i>Morganella sp.</i> | 39 | 97 |
| <i>Providencia sp.</i> | 14 | 79 |
| <i>Serratia sp.</i> | 61 | 89 |
| <i>S. maltophilia</i> | 57 | 96 |

Note: The percent acquired resistance data provided in the above table has been collected from the following countries during the time period specified: US, 1996; Canada, 1993-1994; US/Canada, 1996-1997; France, 1994-1995; US, Arabia, 1994-1995; US, 1996-1997; US, 1991-1993; Belgium, 1993-1994; UK, Netherlands, 1989-1995.

Resistance can vary from region to region and information on local resistance should be taken into account.

Table 4 - MIC Interpretive Standards ($\mu\text{g/mL}$) according to NCCLS guidelines (M100-S10) for amoxicillin and amoxicillin/clavulanic acid

| Organisms | Antimicrobial Agents | MIC ($\mu\text{g/mL}$) Interpretive Standards | | |
|---|-----------------------------|---|------|--------------|
| | | S | I | R |
| <i>Enterobacteriaceae</i> | amoxicillin/clavulanic acid | $\leq 8/4$ | 16/8 | $\geq 32/16$ |
| Non-Enterobacteriaceae* | NA | - | - | - |
| <i>Staphylococcus sp.</i> | amoxicillin/clavulanic acid | $\leq 4/2$ | - | $\geq 8/4$ |
| <i>Enterococcus sp.</i> * | NA | - | - | - |
| <i>Haemophilus sp.</i> | amoxicillin/clavulanic acid | $\leq 4/2$ | - | $\geq 8/4$ |
| <i>Streptococcus pneumoniae</i> | amoxicillin | ≤ 2 | 4 | ≥ 8 |
| | amoxicillin/clavulanic acid | $\leq 2/1$ | 4/2 | $\geq 8/4$ |
| <i>Streptococcus sp.</i> other than <i>S. pneumoniae</i> ** | NA | - | - | - |

Note: *No interpretive standards for amoxicillin or amoxicillin/clavulanic acid.

**A streptococcal isolate that is susceptible to penicillin can be considered susceptible to ampicillin, amoxicillin and amoxicillin/clavulanic acid.

The MIC₉₀ data provided in the above table has been collected from the following countries during the time period specified: US: 91-97; UK: Not Stated; France: 94 – 95; Belgium: 93 – 94.

It should be noted that NCCLS breakpoints are reviewed on a regular basis and may be amended according to the data available.

The following in vitro data are available but their clinical significance is unknown.

Table 5- In Vitro Activity of amoxicillin/clavulanic acid

| | N | MIC 90 (µg/mL) |
|---|-------|----------------|
| GRAM POSITIVE AEROBES: | | |
| <i>Enterococcus faecalis</i> | 185 | 1 |
| <i>Staphylococcus aureus</i> | 229 | 1 |
| <i>Staphylococcus aureus</i> (MSSA) | 95 | 1 |
| <i>Staphylococcus aureus</i> (MRSA) | 20 | 16 |
| <i>Staphylococcus epidermidis</i> | 134 | 4 |
| <i>Staphylococcus saprophyticus</i> | 20 | 1 |
| <i>Coagulase negative staphylococci</i> | 83 | 2 |
| <i>Streptococcus agalactiae</i> | 20 | 0.06 |
| <i>Streptococcus pneumoniae</i> | 1,476 | 2 |
| <i>Streptococcus pyogenes</i> | 764 | 0.12 |
| <i>Streptococcus viridans</i> | 20 | 0.5 |
| GRAM NEGATIVE AEROBES: | | |
| <i>Escherichia coli</i> | 325 | 8 |
| <i>Haemophilus influenzae</i> | 2,268 | 2 |
| <i>Haemophilus influenzae</i> (BLN) | 691 | 1 |
| <i>Haemophilus influenzae</i> (BLP) | 271 | 2 |
| <i>Klebsiella pneumoniae</i> | 200 | 4 |
| <i>Klebsiella oxytoca</i> | 34 | 8 |
| <i>Moraxella catarrhalis</i> | 35 | 0.25 |
| <i>Neisseria gonorrhoeae</i> | 35 | 1 |
| <i>Neisseria meningitidis</i> | 10 | 0.06 |
| <i>Proteus mirabilis</i> | 49 | 2 |
| <i>Proteus vulgaris</i> | 11 | 8 |
| GRAM POSITIVE ANAEROBES: | | |
| <i>Clostridium species</i> | 13 | 0.5 |
| <i>Clostridium perfringens</i> | 16 | 0.06 |
| <i>Clostridium difficile</i> | 21 | 2 |
| <i>Peptostreptococcus species</i> | 19 | 0.5 |
| <i>Clostridium perfringens</i> | 16 | 0.06 |
| <i>Clostridium perfringens</i> | 10 | 0.12 |
| <i>Clostridium perfringens</i> | 10 | 0.25 |
| <i>Clostridium difficile</i> | 21 | 2 |
| <i>Clostridium difficile</i> | 10 | 1 |
| <i>Clostridium difficile</i> | 10 | 1 |
| <i>Propionibacterium sp.</i> | 11 | 0.06 |
| <i>Peptostreptococcus</i> and <i>Ruminococcus sp.</i> | 23 | 0.25 |
| <i>Peptostreptococci</i> | 19 | 0.25 |
| <i>Peptostreptococcus sp.</i> | 14 | 1.0 |
| <i>Peptostreptococcus sp.</i> | 19 | 0.5 |
| GRAM NEGATIVE ANAEROBES | | |
| <i>Bacteroides fragilis</i> | 98 | 2 |
| <i>Bacteroides fragilis group</i> | 163 | 4 |
| <i>Fusobacterium species</i> | 23 | 0.125 |
| <i>Bacteroides fragilis</i> | 20 | 4 |
| <i>Bacteroides fragilis</i> | 19 | 2 |
| <i>Bacteroides fragilis</i> | 24 | 2 |
| <i>Bacteroides fragilis</i> | 176 | 1 |
| <i>Bacteroides thetaiotamicron</i> | 14 | 32 |

| | | |
|---|-----|-------|
| <i>Bacteroides vulgatus</i> | 21 | 4 |
| Other <i>Bacteroides</i> sp. of <i>B. fragilis</i> group | 17 | 16 |
| <i>Bacteroides fragilis</i> group | 80 | 8 |
| Non- <i>B. fragilis</i> | 163 | 2 |
| <i>Prevotella</i> sp | 15 | 8 |
| <i>Prevotella</i> , <i>Porphyromonas</i> and <i>Bacteroides</i> sp. | 27 | 0.25 |
| <i>Fusobacterium</i> sp. | 23 | 0.125 |
| <i>Fusobacterium</i> sp. | 14 | 0.125 |
| <i>B. capillosus</i> | 10 | 1 |
| <i>P. bivia</i> | 15 | 2 |
| <i>P. disiens</i> | 13 | 0.25 |

Note: Methicillin resistant strains are resistant to amoxicillin/clavulanic acid tablets.
Proteus vulgaris and Klebsiella species may not be susceptible to amoxicillin/clavulanic acid tablets at concentrations of amoxicillin and clavulanic acid achieved in the plasma. However at concentrations of amoxicillin and clavulanic acid achievable in the urine the majority of strains are susceptible.

Susceptibility Testing

Diffusion Technique

For Kirby-Bauer method of susceptibility testing, a 30 mcg (20 mcg amoxicillin + 10 mcg clavulanic acid) diffusion disc should be used. With this procedure, a report from the laboratory of "Susceptible" indicates that the infecting organism is likely to respond to amoxicillin + clavulanic acid therapy and a report of "Resistant" indicates that the infecting organism is not likely to respond to therapy. An "Intermediate Susceptibility" report suggests that the infecting organism would be susceptible to amoxicillin + clavulanic acid if the infection is confined to tissues or fluids (e.g. urine) in which high antibiotic levels are attained.

Dilution Techniques

Broth or agar dilution methods may be used to determine the minimal inhibitory concentration (MIC) value susceptibility of bacterial isolates to amoxicillin + clavulanic acid. Tubes should be inoculated to contain 10⁴ to 10⁵ organisms/mL or plates "spotted" with 10³ to 10⁴ organisms.

The recommended dilution method employs a constant amoxicillin/ clavulanic acid ratio of 2 to 1 in all tubes with increasing concentrations of amoxicillin. MICs are reported in terms of amoxicillin concentration in the presence of clavulanic acid at constant 2 parts amoxicillin to 1 part clavulanic acid.

Recommended CLAMOXYL Susceptibility Ranges^{1,2}.

| ORGANISMS | RESISTANT | INTERMEDIATE | SUSCEPTIBLE |
|---|-----------|--------------|-------------|
| Gram Negative Enteric Bacteria | ≤ 13 mm | 14-17 mm | ≥ 18 mm |
| <i>Staphylococcus</i> ³ and <i>Haemophilus</i> <i>spp</i> | ≤ 19 mm | ----- | ≥ 20 mm |

1. The non-β-lactamase-producing organisms which are normally susceptible to ampicillin, such as Streptococci, will have similar zone sizes as for ampicillin discs.
2. The quality control cultures should have the following assigned daily ranges for amoxicillin + clavulanic acid:

| Discs | | Mode MIC (mg/L) |
|------------------------------|---------|----------------------|
| <i>E. coli</i> (ATCC25922) | 19-25mm | 4/2 - 8/4 |
| <i>S. aureus</i> (ATCC25923) | 28-36mm | 0.25/0.12 - 0.5/0.25 |
| <i>E. coli</i> (ATCC35218) | 18-22mm | 4/2 - 8/4 |

The Mode MIC is expressed as the concentration of amoxicillin/clavulanic acid.

3. Organisms which show susceptibility to amoxicillin + clavulanic acid but are resistant to methicillin/oxacillin should be considered resistant.

CLINICAL TRIALS

Amoxicillin and clavulanic acid (875/125 mg) vs amoxicillin and clavulanic acid (500/125 mg): Three pivotal studies in 1,361 patients treated for between 7 and 14 days for either lower respiratory tract infections, upper respiratory infections or complicated urinary tract infections compared a regimen of amoxicillin and clavulanic acid (875/125 mg) tablets every 12 hours (q12h) to amoxicillin and clavulanic acid (500/125 mg) tablets dosed every 8 hours (q8h) (584, 170 and 607 patients, respectively). Comparable efficacy was demonstrated between the q12h and q8h dosing regimens. There was no significant difference in the percentage of adverse events in each group. The most frequently reported adverse event in two of the studies was diarrhoea; incidence rates were similar for the 875/125 mg q12h and 500/125 mg q8h dosing regimens (14.9% and 14.3%, respectively). However, there was a statistically significant difference ($p < 0.05$) in rates of severe diarrhoea or withdrawals with diarrhoea between the regimens: 1.0% for 875/125 mg q12h dosing versus 2.5% for the 500/125 mg q8h dosing. In the third study the most frequently reported adverse event was headache with an incidence of 5.7% (amoxicillin and clavulanic acid q8h) vs 8.3% (amoxicillin and clavulanic acid q12h).

As noted previously although there was no significant difference in the percentage of adverse events in each group there was a statistically significant difference in rates of severe diarrhoea or withdrawals with diarrhoea between the regimens.

Amoxicillin and clavulanic acid (500/125 mg) vs amoxicillin and clavulanic acid (250/125 mg): Two pivotal studies in 908 patients treated for between 5 and 10 days for either uncomplicated Skin and Skin Structure Infections or Acute Exacerbation of Chronic Bronchitis compared a regimen of amoxicillin and clavulanic acid (500/125 mg) tablets every 12 hours with amoxicillin and clavulanic acid (250/125 mg) tablets every 8 hours. Comparable efficacy was demonstrated between the 12 hourly and 8 hourly dosing regimens.

There was no significant difference in the percentage of adverse events in each group, with the most frequently reported adverse event in the two studies being diarrhoea.

The clinical efficacy of amoxicillin and clavulanic acid tablets given in a twice daily versus three times daily regimen have been shown to be comparable in AECS and SSSI, despite the differences in some pharmacokinetic parameters.

Given the similar T_{MIC} and the demonstration of equivalence between AECS and SSSI it would be reasonable to extrapolate to the remaining indications. Clinical safety and efficacy in other indications were investigated, however these supportive studies were not sufficiently designed to demonstrate the relative efficacy of the two amoxicillin and clavulanic acid regimens, or compared the proposed regimen with other treatments.

INDICATIONS

CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) and CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablets are indicated for short term treatment of bacterial infections at the following sites when caused by sensitive organisms (see **PHARMACOLOGY - Microbiology**):

Urinary Tract Infections (uncomplicated and complicated)

Lower Respiratory Tract Infections, including community acquired pneumonia and acute exacerbations of chronic bronchitis

Upper Respiratory Tract Infections, such as sinusitis, otitis media and recurrent tonsillitis.

Skin and Skin Structure Infection

Appropriate culture and susceptibility studies should be performed to identify the causative organism(s) and determine its (their) susceptibility to CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) or CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablets. However, when there is reason to believe an infection may involve any of the β -lactamase producing organisms listed above, therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies. Once these results are known, therapy should be adjusted if appropriate.

The treatment of mixed infections caused by amoxicillin susceptible organisms and β -lactamase producing organisms susceptible to CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) or CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablets should not require the addition of another antibiotic due to the amoxicillin content of CLAMOXYL DUO FORTE 875/125 and CLAMOXYL DUO 500/125.

CONTRAINDICATIONS

A history of allergic reaction to β -lactams (e.g. penicillins or cephalosporins) is a contraindication.

CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) and CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablets are contraindicated in patients with a previous history of amoxicillin/clavulanic acid-associated jaundice or hepatic dysfunction.

PRECAUTIONS

Before initiating therapy with amoxicillin-clavulanate, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens.

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, CLAMOXYL DUO FORTE 875/125 (AMOXYCILLIN AND CLAVULANIC ACID) OR CLAMOXYL DUO 500/125 (AMOXYCILLIN AND CLAVULANIC ACID) TABLETS SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH ADRENALINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including amoxicillin. A toxin produced with *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However in moderate to severe cases appropriate therapy with a suitable oral antibiotic agent effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy.

Since CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) and CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) contain amoxicillin, an aminopenicillin, these are not the treatment of choice in patients presenting with sore throat or pharyngitis because of the possibility that the underlying cause is infectious mononucleosis, in the presence of which there is a high incidence of rash if amoxicillin is used.

CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) and CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablets should be given with caution to patients with lymphatic leukaemia since they are especially susceptible to amoxicillin induced skin rashes.

Amoxicillin-clavulanate should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

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

Abnormal prolongation of prothrombin time (increased INR) has been reported rarely in patients receiving amoxicillin-clavulanate and oral anticoagulants. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Aerobacter*, *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Hepatitis and cholestatic jaundice have been reported rarely. These events have been noted with other penicillins and cephalosporins. Hepatic events subsequent to CLAMOXYL (amoxicillin and clavulanic acid) have been reported predominantly in males and elderly patients and may be associated with prolonged treatment.

Cholestatic hepatitis, which may be severe but is usually reversible, has been reported rarely. Signs and symptoms may not become apparent until several weeks after treatment has ceased. In most cases resolution has occurred with time. However, in extremely rare circumstances, deaths have been reported. These have almost always been cases associated with serious underlying disease or concomitant medications. Hepatic events subsequent to CLAMOXYL (amoxicillin and clavulanic acid) have occurred predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children.

CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) and CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablets should be used with care in patients with evidence of hepatic dysfunction.

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 **OVERDOSAGE**).

CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) tablets should not be used in patients with moderate to severe renal impairment (creatinine clearance ≤ 30 mL/min).

CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablets should be used with care in patients with moderate or severe renal impairment. The dosage of CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) should be adjusted as recommended in the **DOSAGE AND ADMINISTRATION** section.

Carcinogenicity

Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Genotoxicity

The genotoxic potential of amoxicillin and clavulanic acid was investigated in assays for chromosomal damage (mouse micronucleus test and a dominant lethal test) and gene conversion. All were negative.

Effects on Fertility

Amoxicillin and clavulanic acid at oral doses of up to 1200 mg/kg/day had no effect on fertility and reproductive performance in rats dosed with a 2:1 ratio formulation of amoxicillin and clavulanate.

Use in Pregnancy (Category B1)

Animal studies with orally and parenterally administered amoxicillin and clavulanic acid have shown no teratogenic effects. There is limited experience of the use of CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) and CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablets in human pregnancy. In women with preterm, premature rupture of the foetal membrane (pPROM), prophylactic treatment with CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) or CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) 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 Labour and Delivery

Oral ampicillin class antibiotics are generally poorly absorbed during labour. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) or CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablets in humans during labour or delivery has immediate or delayed adverse effects on the foetus, prolongs the duration of labour or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Use in Lactation

Amoxicillin is excreted in the milk; there are no data on the excretion of clavulanic acid in human milk. Therefore, caution should be exercised when CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) or CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablets are administered to a nursing woman.

Effects on Ability to Drive and Use Machines

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

Effects on Laboratory Tests

Oral administration of CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) or CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablets will result in high urine concentrations of amoxicillin. Since high urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest, Benedict's Solution or Fehling's Solution, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix® or Testape®) be used.

Following administration of ampicillin to pregnant women a transient decrease in plasma concentration of total conjugated oestriol, oestriol-glucuronide, conjugated oestrone and oestradiol has been noted. This effect may also occur with amoxicillin, and therefore CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) or CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablets.

INTERACTIONS WITH OTHER MEDICINES

Probenecid decreases the renal tubular secretion of amoxicillin but does not affect clavulanic acid excretion. Concurrent use with CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) or CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablets may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) or CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablets and allopurinol administered concurrently.

No information is available about the concurrent use of CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) or CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablets and alcohol. However, the ingestion of alcohol whilst being treated with some other beta-lactam antibiotics has precipitated a disulfiram (Antabuse) like reaction in some patients. Therefore the ingestion of alcohol should be avoided during and for several days after treatment with CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) or CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid).

In common with other broad spectrum antibiotics, CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) and CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablets may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives. Patients should be warned accordingly.

In the literature there are rare cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin.

In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid of approximately 50% has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure.

ADVERSE EFFECTS

CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) and CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) are generally well tolerated. The majority of events were of a mild and transient nature.

Clinical Trials

During clinical trials, the most frequently reported adverse events related or possibly related to CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) tablets therapy were diarrhoea (14.9%), nausea (7.9%), headache (6.8%), abdominal pain (4.5%), vomiting (3.8%), genital moniliasis (3.6%) and vaginitis (3.4%).

The following adverse events have been observed during clinical trials with CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) tablets; however it should be noted that causality has not necessarily been established for these events:

The most frequently ($\geq 1\%$) reported adverse experiences in decreasing order for the BD regimen

| | 875/125 mg q12hr |
|---------------------------------|-------------------------|
| Total Number of Patients | 584 |
| Adverse Event | Frequency (%) |
| Diarrhoea | 14.9 |
| Nausea | 7.9 |
| Headache | 6.8 |
| Abdominal pain | 4.5 |
| Vomiting | 3.8 |
| Genital moniliasis | 3.6 |
| Vaginitis | 3.4* |
| Back Pain | 1.9 |
| Dizziness | 1.7 |
| Fungal infection | 1.7 |
| Rash | 1.5 |
| Sinusitis | 1.4 |
| Fatigue | 1.2 |
| Genital pruritus | 1.2 |
| Injury | 1.0 |
| Pain | 1.0 |
| Urinary tract infection | 1.0 |
| Insomnia | 1.0 |
| Myalgia | 1.0 |

During clinical trials, the most frequently reported adverse events related or possibly related to CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablets therapy were diarrhoea (12.8%), nausea (5.2%), headache (4.8%), abdominal pain (4.5%).

The following adverse events have been observed during clinical trials with CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablets; however it should be noted that causality has not necessarily been established for these events:

The most frequently ($\geq 1\%$) reported adverse experiences in decreasing order for the BD regimen

| | 500/125 mg q12hr |
|---------------------------------|-------------------------|
| Total Number of Patients | 462 |
| Adverse Event | Frequency (%) |
| Diarrhoea | 12.8 |
| Nausea | 5.2 |
| Headache | 4.8 |
| Upper Respiratory Infection | 1.9 |
| Genital moniliasis | 1.9 |
| Vomiting | 1.5 |
| Dyspepsia | 1.1 |
| Injury | 1.1 |

Post Marketing

In addition, the following adverse reactions have been reported for ampicillin class antibiotics and may occur with CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) and CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) tablets:

very common $\geq 1/10$

common $\geq 1/100$ and $< 1/10$

| | |
|-----------|-------------------------------|
| uncommon | $\geq 1/1000$ and $< 1/100$ |
| rare | $\geq 1/10000$ and $< 1/1000$ |
| very rare | $< 1/10000$ |

Infections and Infestations

Common: mucocutaneous candidiasis

Gastro-intestinal

Very common: diarrhoea

Common: nausea, vomiting

Uncommon: indigestion

Rare: gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis and antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) (see **PRECAUTIONS**).

Hepatobiliary

Uncommon: moderate rise in AST and/or ALT.

Rare: hepatitis, cholestatic jaundice which may be severe but is usually reversible.

Nervous system disorders

Uncommon: dizziness, headache

Very rare: reversible hyperactivity, convulsions. Convulsions may occur in patients with impaired renal function or those receiving high doses.

Haematopoietic and lymphatic systems

Uncommon: thrombocytosis.

Rare: anaemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, reversible leukopenia (including neutropenia or agranulocytosis) - these are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena; prolongation of bleeding time and prothrombin time.

Hypersensitivity and skin

Common: skin rashes, pruritis, urticaria

Rare: angioneurotic oedema, anaphylaxis, serum-sickness-like syndrome, erythema multiforme, Stevens-Johnson syndrome, hypersensitivity, vasculitis, toxic epidermal necrolysis, bullous exfoliative dermatitis and acute generalised exanthematous pustulosis (AGEP) have been reported rarely. Whenever such reactions occur, CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) or CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablets should be discontinued, unless in the opinion of the physician no alternative treatment is available and continued use of this medicine is considered essential. Serious and occasional fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema can occur with oral penicillins (see **PRECAUTIONS**).

Renal and urinary disorders

Rare: interstitial nephritis

Very rare: crystalluria (see **OVERDOSAGE**)

Miscellaneous

Rare: superficial tooth discolouration which can usually be removed by brushing.

DOSAGE AND ADMINISTRATION

CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) and CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) tablets should be taken immediately before or with the first mouthful of food, to minimise potential gastrointestinal intolerance and to optimise absorption.

Adults: The usual adult dose is one CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablet every 12 hours. For more severe infections, the dose should be one CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) tablet every 12 hours.

Note: Though both CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) and CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), two CLAMOXYL DUO 500/125 tablets are not equivalent to one CLAMOXYL DUO FORTE tablet. Therefore, two CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablets should not be substituted for one CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) tablet for the treatment of more severe infections.

Treatment should usually be continued for 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. Treatment should not exceed 14 days without review.

Adults with Impaired Renal Function: Both amoxicillin and clavulanic acid are excreted by the kidneys and the serum half life of each increases in patients with renal failure.

CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) tablets should not be used in patients with moderate to severe renal impairment (creatinine clearance \leq 30 mL/min).

No adjustment to the initial CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) dose is necessary, but the dosing interval should be extended according to the degree of renal impairment.

The following schedule is proposed for CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid):

| | |
|--|---|
| Mild Impairment: (Creatinine clearance >30 mL/min) | No change in dosage. |
| Moderate Impairment: (Creatinine clearance 10 – 30 mL/min) | One CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablet every 12 hours. |
| Severe Impairment: (Creatinine clearance <10 mL/min) | One CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablet every 24 hours. |

Haemodialysis decreases serum concentrations of both amoxicillin and clavulanic acid and an additional dose should be administered at the end of dialysis.

Adults with Impaired Hepatic Function: Data is currently insufficient for a dosage recommendation. Dose with caution, and monitor hepatic function at regular intervals.

Children: Children weighing 40 kg and more should be dosed according to the adult recommendations. It is recommended that CLAMOXYL 125/31.25 (amoxicillin and clavulanic acid) syrup or CLAMOXYL DUO 400/57 (amoxicillin and clavulanic acid) suspension be used for children weighing less than 40 kg (for more information refer to the Product Information document for CLAMOXYL 125/31.25 and CLAMOXYL DUO 400/57).

OVERDOSAGE

Serious and severe clinical symptoms are unlikely to occur after overdosage with CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) or CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablets. If encountered, 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.

Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see **PRECAUTIONS**).

Amoxicillin may be removed from the circulation by haemodialysis.

Contact the Poisons Information Centre (telephone 13 11 26) for further advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) and CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) tablets should be stored below 25°C and protected from moisture.

CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) tablets: Each film coated tablet contains 875 mg amoxicillin as the trihydrate and 125 mg clavulanic acid as the potassium salt. Available in blister packs of 10 and 60*.

CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablets: Each film coated tablet contains 500 mg amoxicillin as the trihydrate and 125 mg clavulanic acid as the potassium salt. Available in blister packs of 10 and 60*.

* Not marketed in Australia

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 - Prescription Only Medicine

DATE OF FIRST INCLUSION ON THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

CLAMOXYL DUO FORTE 875/125 (amoxicillin and clavulanic acid) tablets: 27/10/1998

CLAMOXYL DUO 500/125 (amoxicillin and clavulanic acid) tablets: 15/11/2007

DATE OF MOST RECENT AMENDMENT

23/01/2014