**Amoxicillin + clavulanic acid**

**Section:** 6. Anti-infective medicines → 6.2. Antibacterials → 6.2.1. Access group antibiotics

<table>
<thead>
<tr>
<th>Indication</th>
<th>Infectious cystitis</th>
<th>ICD11 code: GC80.1</th>
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</thead>
<tbody>
<tr>
<td>INN</td>
<td>Amoxicillin + clavulanic acid</td>
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<tr>
<td>Medicine type</td>
<td>Chemical agent</td>
<td></td>
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<tr>
<td>Antibiotic groups</td>
<td>ACCESS</td>
<td></td>
</tr>
<tr>
<td>List type</td>
<td>Core (EML) (EMLc)</td>
<td></td>
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</tbody>
</table>
| Formulations | Parenteral > General injections > IV: 500 mg (as sodium salt) + 100 mg (as potassium salt) powder for injection; 1000 mg (as sodium salt) + 200 mg (as potassium salt) powder for injection.
Oral > Liquid: 125 mg (as trihydrate) + 31.25 mg (as potassium salt) / 5 mL powder for oral liquid (EMLc); 250 mg (as trihydrate) + 62.5 mg (as potassium salt) / 5 mL powder for oral liquid (EMLc).
Oral > Solid > dispersible tablet: 200 mg (as trihydrate) + 28.5 mg (as potassium salt) (EMLc); 250 mg (as trihydrate) + 62.5 mg (as potassium salt) (EMLc).
Oral > Solid > tablet: 500 mg (as trihydrate) + 125 mg (as potassium salt); 875 mg (as trihydrate) + 125 mg (as potassium salt) (EMLc). |
| EML status history | First added in 2017 (TRS 1006)
Changed in 2023 (TRS 1049) |
| Sex | All |
| Age | Also recommended for children |
| Therapeutic alternatives | The recommendation is for this specific medicine |
| Patent information | Patents have expired in most jurisdictions
Read more about patents. |
| Wikipedia | Amoxicillin + clavulanic acid |
| DrugBank | Amoxicillin,
Clavulanic acid (Clavulanate) |

**Expert Committee recommendation**

1. Application for the addition of amoxicillin + clavulanic acid 200 mg + 28.5 mg dispersible tablet to the core list of the EMLc for the same indications for which other formulations of amoxicillin + clavulanic acid are currently listed. The Expert Committee recognized the importance of age-appropriate formulations of essential medicines to better meet the dosing needs of children. The Committee noted that the 7:1 ratio of amoxicillin to clavulanic acid is associated with similar efficacy to the 4:1 ratio but has a reduced frequency of gastrointestinal adverse effects. The dispersible tablet formulation also offers advantages over oral liquid formulations for ease of administration and heat stability. The Committee therefore recommended the inclusion of the 200 mg + 28.5 mg dispersible tablet formulation of amoxicillin + clavulanic acid as an Access group antibiotic on the core list of the EMLc for treatment of bacterial infections in children – specifically those infections for which amoxicillin + clavulanic acid is already recommended on the EMLc. ==

2. Review of the age-appropriateness of formulations of essential medicines for children. In consideration of the review of the age appropriateness of formulations of medicines on the EMLc, and the comparison report of the EML versus EMLc, the Expert Committee recommended changes to the EMLc for addition of new, age-appropriate formulations and strengths of existing essential medicines, deletion of unavailable or age-inappropriate formulations and strengths, and other listing modifications as proposed in the application. The Committee also endorsed the proposals for further review of the public...
Results of the three studies mentioned above were pooled in a subgroup analysis in a 2013 Cochrane

1. Application for the addition of amoxicillin + clavulanic acid 200 mg + 28.5 mg dispersible tablet to the core list of the EMLc for the same indications for which other formulations of amoxicillin + clavulanic acid are currently listed. The public health relevance of age-appropriate formulations of essential medicines for children is well established. The Global Accelerator for Paediatric Formulations was developed in response to the World Health Assembly resolution 69.20 on promoting innovation and access to high quality medicines for children. In the 2022–2024 strategy, the Global Accelerator for Paediatric Formulations clearly stated that the development of dispersible tablets over bulky syrups or the enabling of formulary consolidation with flexible dosage forms should be one of the priority tasks (2). Multiple amoxicillin + clavulanic acid formulations in a 4:1 ratio are included on the EMLc as first- or second-choice empiric treatment for various bacterial infections. • First choice: community-acquired pneumonia, complicated intra-abdominal infections, hospital acquired pneumonia, low-risk febrile neutropenia, lower urinary tract infections, sinusitis, and skin and soft tissue infections. • Second choice: bone and joint infections, community-acquired pneumonia, otitis media and surgical prophylaxis. In 2021, a higher strength formulation of amoxicillin + clavulanic acid in a 7:1 ratio (875 mg + 125 mg) was recommended for inclusion on the EML for treatment of community-acquired pneumonia and intra-abdominal infections in adults. In making its recommendation, the Expert Committee noted that a higher ratio of amoxicillin to clavulanic acid is generally associated with less diarrhoea, a recognized adverse effect of this combination (1). Amoxicillin + clavulanic acid 200 mg + 28.5 mg dispersible tablet is not currently available in any markets. It has regulatory approval in Malawi. Submissions made to regulatory authorities for Kenya, Rwanda and Uganda are pending approval. =========

Summary of evidence

1. Application for the addition of amoxicillin + clavulanic acid 200 mg + 28.5 mg dispersible tablet to the core list of the EMLc for the same indications for which other formulations of amoxicillin + clavulanic acid are currently listed. The evidence of benefits presented by the applicants was mostly based on studies from the 1990s when the formulation of amoxicillin + clavulanic acid at a 7:1 ratio was first developed. No specific evidence on the efficacy of the dispersible formulation was included. A randomized, observer-blinded, multicentre study conducted in the 1990s evaluated the efficacy of amoxicillin + clavulanic acid as twice daily dosing at a 7:1 ratio compared with three times daily dosing at a 4:1 ratio in 463 children, aged 2–12 years with acute otitis media (3). The two treatment groups demonstrated similar efficacy with clinical success rates at the end of therapy (10 days) of 91.8% for the twice-daily 7:1 group versus 90.5% for the three-times-daily 4:1 group. No significant difference was seen between treatment groups in the incidence of adverse events, however the incidence of diarrhoea was lower in the twice-daily group (6.7% versus 10.3%) group. Significantly more patients in the twice-daily group than the three-times-daily group were reported to have at least 80% compliance with treatment. Another United States study from the 1990s randomized 868 children aged 2–12 years with acute otitis media to receive amoxicillin (45 mg) + clavulanic acid (6.4 mg) twice daily for 10 days, 40/10 mg three times daily for 10 days or 45/6.4 mg twice daily for 5 days (4). Treatment successes (clinical cure or improvement) were reported as 86.5%, 78.7% and 71.1% in the three treatment groups, respectively. The incidence of diarrhoea was significantly greater in the three-times daily group (26.7%), than in the two twice-daily groups (9.6% and 8.7%). A third randomized study from the 1990s of 415 children aged 2 months to 12 years with acute otitis media compared amoxicillin + clavulanic acid twice daily in a 7:1 ratio with three times daily in a 4:1 ratio given for 7 or 10 days (5). At the end of therapy (days 7–12), clinical success (cure) was achieved by about 94% of patients in both treatment groups. At follow-up (days 38–42), 93.3% of patients in the twice-daily group and 87.9% in the three-times-daily group continued to have a clinically successful response. Both treatment regimens were well tolerated, with most adverse events being of a mild-to-moderate and transient nature. Diarrhoea was reported in 7.2% and 10.7% of the twice-daily and three-times daily groups, respectively. Compliance with treatment was reported as 82.8% in the twice-daily group and 73.3% in the three-times-daily group. Results of the three studies mentioned above were pooled in a subgroup analysis in a 2013 Cochrane systematic review (6). No significant differences were found between once- or twice- daily groups and the three-times daily group.
for: clinical cure rate at the end of therapy (risk ratio (RR) 1.03, 95% confidence interval (CI) 0.99 to 1.07); clinical cure rate during therapy (RR 1.00, 95% CI 0.70 to 1.42); clinical cure rate at post-treatment (RR 1.04, 95% CI 0.98 to 1.10); recurrent infection after completion of therapy (RR 1.01, 95% CI 0.39 to 2.60); overall adverse reactions (RR 0.92, 95% CI 0.52 to 1.63); diarrhoea (RR 0.70, 95% CI 0.48 to 1.00); skin adverse events (RR 0.72, 95% CI 0.44 to 1.17) or compliance rate (RR 1.05, 95% CI 0.98 to 1.13). An observer-blinded, multicentre study conducted in the 1990s randomized 437 children aged 2–12 years with lower respiratory tract infections to receive 7 days of treatment with amoxicillin + clavulanic acid either twice daily in a 7:1 ratio or three times daily in a 4:1 ratio (7). Both regimens had similar clinical success (cure) rates (81.0% and 77.8%, respectively). Both regimens were well tolerated, and no statistically significant difference was found in the incidence of adverse events between the two groups. Compliance with study medication was high and similar for both groups (80% compliance was 90.0% and 87.0% for the twice-daily and three-times-daily groups, respectively). The safety profile of amoxicillin + clavulanic acid is well known. In children, the most frequently reported adverse events are mild gastrointestinal disturbances, with diarrhoea being largely attributed to clavulanic acid. In the trials with a direct comparison between amoxicillin + clavulanic acid 4:1 versus 7:1 ratios, no significant difference was seen in the safety profile of the two products overall. Some trials reported a significantly lower incidence of diarrhoea in the twice-daily 7:1 groups, which is plausible due to the lower dose of clavulanic acid administered (3,4,8). The price of the proposed product is reported in the application as US$ 2.05 per pack of 32 dispersible tablets (US$ 0.064 per tablet). Indicative prices for amoxicillin + clavulanic acid 4:1 formulations included in the UNICEF supply catalogue are: • 250 mg/62.5 mg dispersible tablet: US$ 5.06 per pack of 50 tablets (US$ 0.10 per tablet); • 125 mg/31.25 mg powder for oral suspension: US$ 1.87 per 100 mL bottle (US$ 0.09 per 125 mg amoxicillin dose).
**First choice**
- trimethoprim
- nitrofurantoin
- sulfamethoxazole + trimethoprim
- amoxicillin + clavulanic acid

**Second choice**

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