# Nitrofurantoin

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

EMLc | ATC codes: J01XE01

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| **Indication** | Infectious cystitis ICD11 code: GC00.1 |
| **INN** | Nitrofurantoin |
| **Medicine type** | Chemical agent |
| **Antibiotic groups** | A ACCESS |
| **List type** | Core |
| **Formulations** | **Oral > Liquid:** 25 mg per 5 mL oral liquid (EMLc)<br>**Oral > Solid > dosage form:** 100 mg ; 50 mg (EMLc) |
| **EML status history** | First added in 1979 (TRS 641)<br>Changed in 1997 (TRS 882)<br>Changed in 2007 (TRS 950)<br>Changed in 2017 (TRS 1006)<br>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<br>Read more about patents. |
| **Wikipedia** | Nitrofurantoin |
| **DrugBank** | Nitrofurantoin |

## 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 health relevance and

evidence for specific medicines for use in children for potential future consideration for inclusion on the EMLc. The Committee noted and welcomed the ongoing review being coordinated by the Secretariat for the remaining sections of the EMLc for consideration by the 2025 Expert Committee. As a result of the review of the age-appropriateness of formulations on the EMLc, the Expert Committee recommended: - the addition of a new formulation of amoxicillin + clavulanic acid (dispersible tablet 250 mg + 62.5 mg) to the EMLc. - the addition of a new strength formulation of nitrofurantoin (solid oral dosage form 50 mg) on the EMLc. - the addition of a new strength formulation of sulfamethoxazole + trimethoprim (dispersible tablet 100 mg + 20 mg) on the EMLc.

## Background

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.
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## 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). =======

## Guidelines

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 WHO AWaRe (Access, Watch, Reserve) antibiotic book (9) provides guidance on the prescribing and use of antibiotics on the WHO Model Lists of Essential Medicines for the empiric treatment of common infections in adults and children. It reflects the recommendations for essential antibiotics made by the WHO Expert Committee on Selection and Use of Essential Medicines, incorporating the principles of the WHO AWaRe classification of antibiotics. =======

## Committee considerations

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 Global Coordination and Partnership department within the Antimicrobial Resistance division reviewed and provided comments on the application, indicating its support for the addition of the proposed new dispersible tablet formulation of amoxicillin + clavulanic on the EMLc. The EML Antimicrobial Working Group reviewed the application and advised that it supports the inclusion of amoxicillin + clavulanic acid dispersible tablets at a 7:1 ratio (200 mg + 28.5 mg) on the EMLc. The Working Group noted that the 7:1 dispersible tablets proposed in the application offer several advantages over currently listed paediatric formulations such as ease of administration and heat stability at a similar price. The oral liquid formulations currently listed on the Model Lists must be refrigerated after reconstitution which is a challenge in many resource-constrained settings. The Working Group acknowledged that amoxicillin + clavulanic acid was identified as one of the priority antibiotics during the WHO meeting on paediatric drug optimization for antibiotics in November–December 2022. While UNICEF currently

procures amoxicillin + clavulanic acid dispersible tablets at a 4:1 ratio (250 mg + 62.5 mg), which is also being proposed for inclusion on the EMLc as part of the EMLc formulation review in the context of the Global Accelerator for Paediatric Formulations project, it was considered that the additional availability of a dispersible tablet at a 7:1 ratio may offer certain advantages. These advantages include allowing higher doses of amoxicillin without dose-related side-effects associated with a higher clavulanic acid dose (e.g. in settings where penicillin non-susceptible pneumococci are prevalent). The Working Group noted that the dispersible tablets proposed in this application did not receive regulatory approval from the European Medicines Agency as they did not meet its requirement of disintegration within 3 minutes, an issue which does not seem to affect hospital or community use or offset the key advantages. Given the public health need for this formulation, the Working Group did not consider this should preclude its addition to the EMLc. =======

## EML recommendations: Infectious cystitis

| First choice | Second choice |
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| trimethoprim | |
| nitrofurantoin | |
| sulfamethoxazole + trimethoprim | |
| amoxicillin + clavulanic acid | |

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.

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2021 (including the 22nd WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2021 (WHO Technical Report Series, No. 1035; https://iris.who.int/handle/10665/351172, accessed 6 October 2023).
2. Shaping the global innovation and access landscape for better paediatric medicines: Global Accelerator for Paediatric Formulations 2022–2024 business plan. Geneva: World Health Organization; 2022 (https://iris.who.int/handle/10665/362635, accessed 6 October 2023).
3. Behre U, Burow HM, Quinn P, Cree F, Harrison HE. Efficacy of twice-daily dosing of amoxycillin/clavulanate in acute otitis media in children. Infection. 1997;25(3):163–6.
4. Hoberman A, Paradise JL, Burch DJ, Valinski WA, Hedrick JA, Aronovitz GH, et al. Equivalent efficacy and reduced occurrence of diarrhea from a new formulation of amoxicillin/clavulanate potassium (Augmentin) for treatment of acute otitis media in children. Pediatr Infect Dis J. 1997;16(5):463–70.
5. Damrikarnlert L, Jauregui AC, Kzadri M. Efficacy and safety of amoxycillin/clavulanate (Augmentin) twice daily versus three times daily in the treatment of acute otitis media in children. The Augmentin 454 Study Group. J Chemother. 2000;12(1):79–87.
6. Thanaviratananich S, Laopaiboon M, Vatanasapt P. Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media. Cochrane Database Syst Rev. 2013(12):CD004975.
7. Cook RC, Zachariah J, Cree F, Harrison HE. Efficacy of twice-daily amoxycillin/clavulanate ('Augmentin-Duo' 400/57) in mild to moderate lower respiratory tract infection in children. Br J Clin Pract. 1996;50(3):125–8.
8. Calver AD, Walsh NS, Quinn PF, Baran C, Lonergan V, Singh KP, et al. Dosing of amoxicillin/clavulanate given every 12 hours is as effective as dosing every 8 hours for treatment of lower respiratory tract infection. Lower Respiratory Tract Infection Collaborative Study Group. Clin Infect Dis. 1997;24(4):570–4.
9. The WHO AWaRe (Access, Watch, Reserve) antibiotic book. Geneva: World Health Organization; 2022 (https://iris.who.int/handle/10665/365237, accessed 6 October 2023).

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