Phenoxymethylpenicillin

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

EMLc | ATC codes: J01CE02

Indication	Bacterial pneumonia ICD11 code: CA40.0Z
INN	Phenoxymethylpenicillin
Medicine type	Chemical agent
Antibiotic groups	A ACCESS
List type	Core
Formulations	**Oral > Liquid:** 250 mg per 5 mL (as potassium salt) powder for oral liquid **Oral > Solid:** 250 mg (as potassium salt) ; 500 mg (as potassium salt) (EML)
EML status history	First added in 2017 (TRS 1006) Changed in 2021 (TRS 1035)
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	Phenoxymethylpenicillin
DrugBank	Phenoxymethylpenicillin

Expert Committee recommendation

1. Application to include new higher strength formulations of various antibiotics currently included on the EML to better align with the dosing needs of adults. The Expert Committee recommended the addition of the new strength formulations of amoxicillin, cefalexin, ceftriaxone, ciprofloxacin, clindamycin, phenoxymethylpenicillin and vancomycin to the existing listings of these medicines on the EML for the indications for which they are proposed. The Committee noted that the proposed strength formulations are higher than those currently included on the Model List, and are appropriate and aligned to meet recommended doses for treatment of adults, with the advantages of a reduced pill burden in the case of oral formulations, and facilitating a simplified and safer dose administration in the case of intravenous formulations. 2. Application to include a new strength formulation (875 mg + 125 mg) of amoxicillin + clavulanic acid on the EML for the treatment of mild community-acquired pneumonia and intra-abdominal infections in adults. The Expert Committee noted that the proposed formulation of amoxicillin + clavulanic acid will provide a higher dose of amoxicillin, without increasing the dose of clavulanic acid, and is particularly suitable for more unwell patients. In addition, the Committee noted that a higher ratio of amoxicillin to clavulanic acid is generally associated with less diarrhoea, a recognized adverse effect of this combination. The addition of this new formulation will also allow recommended amoxicillin doses to be achieved with a reduced pill burden for patients. The Committee therefore recommended the addition of the new strength formulation of amoxicillin + clavulanic acid 875 mg + 125 mg tablets to the core list of the EML for the treatment of mild community-acquired pneumonia and intra-abdominal infections in adults.

Background

1. Application to include new higher strength formulations of various antibiotics currently included on the EML to better align with the dosing needs of adults. The application requested the inclusion of new higher strengths of the following antibiotics on the EML to better align with the dosing needs of adults: Amoxicillin: solid oral dosage form 1 g Cefalexin: solid oral dosage form 500 mg Ceftriaxone: powder for injection 2 g Ciprofloxacin: solid oral dosage form 500 mg Clindamycin: injection 600 mg/4 mL, 900 mg/6 mL Phenoxymethylpenicillin: tablet 500 mg Vancomycin: powder for injection 500 mg, 1 g All of the antibiotics for which additional strength formulations are proposed are currently included on the EML is various other formulations and strengths for the indications described below (1). 2. Application to include a new strength formulation (875 mg + 125 mg) of amoxicillin + clavulanic acid on the EML for the treatment of mild community-acquired pneumonia and intra-abdominal infections in adults. Amoxicillin + clavulanic acid, in multiple formulations, has been included on the Model Lists since 1997. Amoxicillin + clavulanic acid is currently included on the EML and EMLc as a first- or second-choice empiric treatment for several bacterial infections. The EML currently recommends amoxicillin + clavulanic acid as a second-choice option for community-acquired pneumonia because in most cases there is no need to broaden the spectrum of antibacterial activity to cover more resistant pathogens and amoxicillin (or phenoxymethylpenicillin) can safely be used. The other reason is that amoxicillin + clavulanic is associated with more frequent side-effects than amoxicillin alone – mostly diarrhoea, including Clostridioides difficile infection (1). Amoxicillin + clavulanic acid is also recommended in the EML as a first-choice option for the empiric treatment of mild, community-acquired intra-abdominal infections in patients who are not critically ill and there is no suspicion of sepsis or septic shock. Community-acquired pneumonia is common worldwide and is a leading cause of morbidity and mortality, with an especially high burden in low-income countries (2). According to the Global Burden of Disease study, in 2017 among all ages and sexes combined, an estimated 471 million new cases of lower respiratory tract infections (including community-acquired pneumonia) occurred globally (3). The most common causative pathogen worldwide is Streptococcus pneumoniae, and viral co-infection is not unusual. In general, the incidence of community-acquired pneumonia and risk of death increase with age (4). Community-acquired pneumonia is curable and preventable. Most people who develop this infection can be successfully treated with a 5-day antibiotic regimen. Vaccines to prevent community-acquired pneumonia caused by certain pathogens (e.g. Streptococcus pneumoniae, Haemophilus influenzae type b and influenza virus). Intra-abdominal infections include uncomplicated infections with no involvement of the peritoneal cavity and no abscess formation and complicated infections with involvement of the peritoneal cavity and/or abscess formation. The most frequent intraabdominal infections include acute appendicitis, acute cholecystitis, acute cholangitis, acute diverticulitis and pyrogenic liver abscess. Treatment of these infections usually requires a combination of antibiotics and surgery to achieve adequate control of the source of infection.

Summary of evidence

1. Application to include new higher strength formulations of various antibiotics currently included on the EML to better align with the dosing needs of adults. Amoxicillin: solid oral dosage form 1 g Most adult and adolescent patients with mild community-acquired pneumonia or acute bacterial sinusitis can be successfully treated with amoxicillin 1 g every 8 hours for 5 days. The proposed 1 g oral formulation will allow for a reduced pill burden to complete the course of treatment compared with the currently listed 500 mg strength formulation, and should facilitate adherence to treatment. Cefalexin: solid oral dosage form 500 mg Most adult patients diagnosed with exacerbations of chronic obstructive pulmonary disease, can be successfully treated with cefalexin 500 mg every 12 hours for 5 days. For bacterial pharyngitis and mild skin and soft tissue infections, most adult and adolescent patients can be successfully treated with cefalexin 500 mg every 8 hours for 5 days. The proposed 500 mg oral formulation will allow for a reduced pill burden to complete a course of treatment compared with the currently listed 250 mg strength formulation, and should facilitate adherence to treatment. Ceftriaxone: powder for injection 2 g This higher strength formulation is preferable for the treatment of certain infections because it maximizes the chances of bacterial eradication in order to achieve clinical success. For example, in the case of acute bacterial meningitis, a ceftriaxone dose of 2 g every 12 hours is needed to achieve adequate concentrations of the drug in

the central nervous system. The recommended duration of treatment is 10 days. For adult patients with hospital-acquired pneumonia and no risk factors for multidrug-resistant infections, ceftriaxone 2 g a day for 7 days is a recommended treatment regimen. For complicated intra-abdominal infections, ceftriaxone 2 g per day for 5 days (in combination with metronidazole) is a recommended treatment in cases where extended-spectrum beta-lactamase strains are not suspected. For severe cases of enteric fever, if ceftriaxone is used, a dose of 2 g per day for 10 days is recommended. Ciprofloxacin: solid oral dosage form 500 mg The proposed higher strength formulation will benefit adult and adolescent patients prescribed ciprofloxacin for infections including acute invasive bacterial diarrhoea, cholera, complicated intra-abdominal infections, enteric fever, low-risk febrile neutropenia and upper urinary tract infections. Treatment regimens recommend ciprofloxacin doses of 500 mg every 12 hours for 3, 5 or 7 days, depending on the indication or, in the case of cholera, a single dose of 1 g. The proposed 500 mg oral formulation will allow for a reduced pill burden to complete the course of treatment compared with the currently listed 250 mg strength formulation, and should facilitate adherence to treatment. Clindamycin: injection 600 mg/4 mL, 900 mg/6 mL The higher strength formulations of clindamycin are preferable for the treatment of bone and joint infections to maximize the chance of bacterial eradication in order to achieve clinical success. For adults and adolescents diagnosed with osteomyelitis, clindamycin is an acceptable treatment option when methicillin-resistant Staphylococcus aureus (MRSA) is suspected or confirmed when antimicrobial susceptibility of MRSA to clindamycin is proven or likely. Intravenous clindamycin at a dose of 600 mg every 8 hours for 4–6 weeks is a recommended dosage regimen in most cases. Clindamycin may also be used in patients allergic to penicillin. Phenoxymethylpenicillin: solid oral dosage form 500 mg Most adult and adolescent patients with mild community-acquired pneumonia, bacterial pharyngitis or dental infections can be successfully treated with phenoxymethylpenicillin 500 mg every 6 hours for 5 days; however, a longer treatment duration may be recommended in some circumstances. The proposed 500 mg strength oral formulation will allow for a reduced pill burden to complete the course of treatment compared with the currently listed 250 mg strength formulation and should facilitate adherence to treatment. Vancomycin: powder for injection 500 mg, 1 g For adult and adolescent patients with high-risk febrile neutropenia when MRSA infection is suspected, weight-based dosing of vancomycin is recommended (15–20 mg/kg every 12 hours). The 500 mg and 1 g strength formulations will allow for the achievement of recommended dose using fewer vials, compared with the currently listed 250 mg strength. 2. Application to include a new strength formulation (875 mg + 125 mg) of amoxicillin + clavulanic acid on the EML for the treatment of mild community-acquired pneumonia and intra-abdominal infections in adults. Benefits: The rationale for the inclusion of the 875 mg + 125 mg formulation of amoxicillin + clavulanic acid is to increase the amoxicillin to clavulanic acid ratio from 4:1 (500 mg + 125 mg formulation) to 7:1. There is limited evidence about differences in clinical and microbiological efficacy of the different ratios of amoxicillin to clavulanic acid. However, the advantage of the 7:1 ratio formulation is increased exposure to amoxicillin without increased exposure to clavulanic acid. The reason for limiting exposure to clavulanic acid is that increasing its dose exposes patients to a higher risk of gastrointestinal side-effects (especially diarrhoea) with only a minimal increase in efficacy against beta-lactamases (5). Amoxicillin + clavulanic acid is recommended for the treatment of mild community-acquired pneumonia because it is effective against the most likely bacterial pathogens responsible for this syndrome (notably Streptococcus pneumoniae and Haemophilus influenzae, including strains that produce beta-lactamases) and because it is safe, inexpensive and readily available in many settings. In general, amoxicillin alone remains effective against Streptococcus pneumoniae isolates in most cases because these isolates are not known to produce beta-lactam enzymes (5). However, other pathogens (mostly Haemophilus influenzae) produce beta-lactamases in a large proportion of cases (6,7) and could therefore be resistant to amoxicillin alone. Such cases would therefore benefit from treatment with amoxicillin + clavulanic acid. A key element of the treatment of community-acquired pneumonia is to maximize the chance of bacterial eradication in order to achieve clinical success and to reduce the risk of resistance developing. For beta-lactam agents, maximal clinical efficacy depends on the time that the plasma concentration of the drug remains above the level of the minimal inhibitory concentration (MIC) for the target pathogen (T>MIC). For amoxicillin, a T>MIC of at least 30–40% between dosing intervals is required to effectively treat most pathogens responsible of mild community-acquired pneumonia. Therefore, the advantage of a formulation with a higher dose of amoxicillin is that it can improve the efficacy of amoxicillin + clavulanic acid for the treatment of pathogens with higher MICs (8). In particular, the 875 mg +125 mg formulation (given three times a day) would achieve bacteriological efficacy against strains with amoxicillin

MICs of up to 4 mg/L (T>MIC 34% for MICs of 4 mg/L, 57% for MICs of 2 mg/L and 69% for MICs of 1 mg/L), while the 500 mg + 125 mg formulation (three times a day) would only achieve bacteriological efficacy against strains with MICs of up to 2 mg/L (T>MIC 43% for MICs of 2 mg/L and 55% for MICs of 1 mg/L) (9). An additional advantage of amoxicillin + clavulanic acid that applies to both its use for the treatment of mild community-acquired pneumonia and mild community-acquired intra-abdominal infections is its lower potential for resistance compared with other antibiotic options that are sometimes used for the treatment of these syndromes, most notably fluoroquinolones. In patients with community-acquired pneumonia, amoxicillin + clavulanic acid is a particularly valid option in patients who would be at higher risk of poor outcomes if initial empiric treatment were inadequate (e.g. patients with multiple comorbidities who are often more vulnerable to infections or patients with a higher risk of resistant infections due to frequent antibiotic exposure). The clinical and bacteriological efficacy of the 875 mg +125 mg formulation is high (> 90% for clinical efficacy and 80–90% for microbiological efficacy at the end of treatment in trials where this formulation has been used (10)) including in settings with a high prevalence of penicillin-resistant Streptococcus pneumoniae (11). Many patients with intra-abdominal infections may not be able to tolerate oral treatment in the initial phase of treatment, especially those with complicated infections that require surgery; therefore, patients are often started on intravenous treatment. For the treatment of intra-abdominal infections, the use of the 875 mg +125 mg oral formulation of amoxicillin + clavulanic would apply in only certain circumstances: initial empiric treatment of mild cases in patients who can tolerate oral treatment (e.g. patients managed in the outpatient setting) and intravenous to oral switch to complete the course of treatment initiated with intravenous therapy. Amoxicillin + clavulanic acid has a range of antibacterial activity that allows for the coverage of the most likely pathogens responsible for intra-abdominal infections (most notably Escherichia coli, enteric streptococci and anaerobic bacteria) even though amoxicillin + clavulanic resistance rates among E. coli isolates may be of concern in some settings (12). No clinical trial was identified that directly compared the efficacy of different doses of oral amoxicillin + clavulanic acid for intra-abdominal infections. However, the 875 mg + 125 mg oral formulation has been used in several trials, especially for the treatment of uncomplicated acute appendicitis with antibiotics alone (13,14), while lower doses of amoxicillin + clavulanic acid (500 mg + 25 mg) are generally used when treatment is started intravenously and then later switched to oral treatment (15). As detailed above for community-acquired pneumonia, the use of a higher dose of amoxicillin in combination with clavulanic acid, improves efficacy for the treatment of pathogens with higher MICs; therefore, the 875 mg +125 mg is preferable to achieve cure and reduce the risk of resistance developing when oral treatment is chosen. In serious infections, such as intra-abdominal infections, high protein binding of beta-lactams and rapid elimination can reduce the amount of antibiotic available in both the plasma and tissue, increasing the risk of treatment failure, especially in cases of pathogens with higher MICs (16). Therefore, doses should be increased and the interval between doses reduced, especially when oral beta-lactam treatment is used. In order to appropriately treat resistant pathogens, the daily dose of amoxicillin can be more safely increased than the dose of other antibiotics used to treat intra-abdominal infections such as fluoroquinolones. Fluoroquinolones have a worse safety profile, both for gastrointestinal and mild neurological reactions (nausea, vomiting, dizziness, insomnia and headache) but also for more serious adverse events such as tendinitis and tendon rupture (17), risk of arrhythmias (18) or possibly rupture of an aortic aneurysm (19). Harms: Potential harms associated with the 875 mg + 125 mg formulation of amoxicillin + clavulanic acid are not expected to differ from the 500 mg + 125 mg preparation, as the dose of clavulanic acid (responsible for common side-effects such as diarrhoea) remains the same. Moreover, in published trials, even higher doses of amoxicillin + clavulanic acid (2000 mg + 125 mg) have been safely used and were well tolerated (10).

Committee considerations

1. Application to include new higher strength formulations of various antibiotics currently included on the EML to better align with the dosing needs of adults. All proposed formulations are approved by several regulatory agencies including the US Food and Drug Administration and European Medicines Agency, and are available in most countries. 2. Application to include a new strength formulation (875 mg + 125 mg) of amoxicillin + clavulanic acid on the EML for the treatment of mild community-acquired pneumonia and intra-abdominal infections in adults. There are several suppliers of the 875 mg +125 mg formulation globally at a cost of about US$ 10 per

pack (12 tablets) in high-income countries. Amoxicillin + clavulanic acid 875 mg + 125 mg has regulatory approval globally and is available in most countries.

EML recommendations: Bacterial pneumonia

First choice	Second choice
COMMUNITY-ACQUIRED PNEUMONIA - MILD TO MODERATE	
phenoxymethylpenicillin	amoxicillin + clavulanic acid
amoxicillin	doxycycline
COMMUNITY-ACQUIRED PNEUMONIA - SEVERE [CHILDREN]	
ampicillin	
benzylpenicillin	
amoxicillin + clavulanic acid	
cefotaxime	
ceftriaxone	
amoxicillin	
COMMUNITY-ACQUIRED PNEUMONIA - SEVERE	
cefotaxime	amoxicillin + clavulanic acid
ceftriaxone	

1. Application to include new higher strength formulations of various antibiotics currently included on the EML to bet ter align with the dosing needs of adults.

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