

F.2 - Proposal for the addition of a 875 mg amoxicillin + 125 mg clavulanic acid oral formulation to the WHO Model List of Essential Medicines

MSF supports the addition of a (875 mg + 125 mg) amoxicillin + clavulanic acid solid oral dosage form to the core list in section 6.2.1 Access group antibiotics, in the WHO Model List of Essential Medicines (EML). This dosage form is a 7:1 ratio amoxicillin + clavulanic acid dosage form. Amoxicillin is an antibiotic belonging to the beta-lactam family; clavulanic acid is a beta-lactamase inhibitor, added to inhibit the beta-lactamases produced by bacteria to destroy amoxicillin.

Currently, amoxicillin + clavulanic acid is included in the EML, in the core list in section 6.2.1 Access group antibiotics, with different dosage forms: oral liquid and tablets with a 4:1 ratio amoxicillin/clavulanic acid and powder for injection with a 5:1 ratio, for treatment of several bacterial infections.

The application requires that a (875 mg + 125 mg, 7:1 ratio) amoxicillin + clavulanic acid oral dosage form should be included in the EML, as a first choice for mild community-acquired intra-abdominal infections (acute appendicitis, acute cholecystitis, acute cholangitis, acute diverticulitis and pyogenic liver abscess) and as a second choice for mild community-acquired pneumonia, for adult patients.

In the 2019 “Clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America”, the recommended standard regimen in initial treatment of community-acquired pneumonia for adult outpatients with comorbidities is a combination of amoxicillin + clavulanic acid or cephalosporin with a macrolide or doxycycline. The recommended doses of amoxicillin + clavulanic acid depend on the ratio: amoxicillin 500 mg/clavulanic acid 125 mg three times daily, or amoxicillin 875 mg/clavulanic acid 125 mg twice daily. According to this guideline, there is evidence supporting amoxicillin + clavulanic acid in outpatients and inpatients with community-acquired pneumonia.

A narrative review comparing oral amoxicillin and amoxicillin + clavulanic acid published in 2019 by the European Society of Clinical Microbiology and Infectious Diseases recommends that amoxicillin + clavulanic acid be indicated in community-acquired pneumonia of any severity in patients with little/no access to healthcare structures, severe community-acquired

pneumonia and complicated intra-abdominal infection, severe chronic obstructive pulmonary disease exacerbation, surgical site infection, cellulitis, bone and joint infections.

The advantage of the 7:1 ratio formulation is to increase the dose of amoxicillin per dose, therefore per day, while maintaining the same dose of clavulanic acid as in the 4:1 ratio. The efficacy of clavulanic acid against beta-lactamases is not dose-dependent (beta-lactamases are inhibited by low doses of clavulanic acid). The main advantage of the 7:1 ratio for the patients is a better tolerance: the risk of gastro-intestinal side effects is significantly lower than with the 4:1 ratio.

In the treatment of infections in adults, a formulation with a higher dose of amoxicillin, using a 7:1 ratio dosage form reduces the pill burden and improves tolerance, therefore allowing a better adherence to treatment.

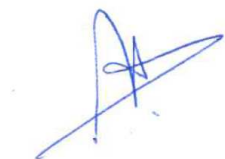
MSF would like to draw the attention of the Expert Committee to the fact that an 8:1 ratio dosage form should also be included in the EMLs, in order to ease supply in all settings.

MSF would like to emphasize that a child-friendly formulation, such as dispersible tablet, should be included in the EML and the EMLc, for paediatric indications. MSF has been using the powder for oral suspension with an 8:1 ratio since 2013 and the dispersible tablet with a 7:1 ratio in its programs since 2018.

MSF has been using both the 7:1 ratio and the 8:1 ratio amoxicillin + clavulanic acid in its programs since 2013, reserving the 4:1 ratio for multidrug resistant tuberculosis programs only (for use in combination with meropenem or imipenem + cilastatin).

In light of these elements, MSF urges the 23rd Expert Committee on the Selection and Use of Essential Medicines to include a (875 mg + 125 mg) amoxicillin + clavulanic acid solid oral dosage form in the core list in section 6.2.1 Access group antibiotics in the WHO Model List of Essential Medicines.

For Médecins Sans Frontières

A handwritten signature in blue ink, appearing to be 'M. Henkens', with a stylized flourish at the end.

Myriam Henkens, MD, MPH
International Medical Coordinator