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F.1 Amoxicillin + clavulanic acid dispersible tablet (200 mg + 28.5 mg)

MSF strongly supports the addition of a (200 mg + 28.5 mg) amoxicillin + clavulanic acid dispersible tablet to the core list in section 6.2.1 “Access group antibiotics”, in the WHO Model List of Essential Medicines for Children (EMLc). This dosage form is a 7:1 ratio amoxicillin + clavulanic acid dosage form.

Currently, amoxicillin + clavulanic acid is included in both the WHO Model List of Essential Medicines (EML) and the WHO Model List of Essential Medicines for Children (EMLc), in the Core List in Section 6.2.1 “Access group antibiotics”, for treatment of several bacterial infections, with different dosage forms; powders for oral liquid and tablets with a 4:1 ratio amoxicillin/clavulanic acid, powders for injection with a 5:1 ratio. Since 2021, a tablet formulation with a 7:1 ratio (875 mg + 125 mg) is also included in the EML.

In 2021, MSF supported 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) and MSF also emphasized that a child-friendly formulation, such as dispersible tablet, should be included in the EML and the EMLc, for paediatric indications. The 23rd Expert Committee on the Selection and Use of Essential Medicines 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.

The application requests the inclusion of a (200 mg + 28.5 mg, 7:1 ratio) amoxicillin + clavulanic acid dispersible tablet in the EMLc, as a therapeutic alternative to amoxicillin + clavulanic acid 4:1 ratio, powder for oral suspension (125 mg + 31.25 mg/5 mL; 250 mg+ 62.5 mg/5mL).

The 2022 WHO AWaRe (Access, Watch, Reserve) Antibiotic Book recommends 80–90 mg/kg/day (amoxicillin component) and twice-daily intake for the treatment of various infections in children. Oral liquid formulations must be refrigerated after reconstitution as clavulanic acid is rapidly degraded in high ambient temperatures. The indications listed are: acute otitis media, acute sinusitis, urinary tract infection, skin and soft tissue infections (mild) and febrile neutropenia (low risk), intra-abdominal infections (mild), bone and joint infections, hospital-acquired pneumonia, periorbital cellulitis, pyomyositis. The Antibiotic Book states also that in empiric antibiotic treatment for lower urinary tract infections, Escherichia coli resistance rates to amoxicillin + clavulanic acid are lower than to amoxicillin alone. This combination still has activity against some extended-spectrum beta-lactamase-producing isolates and it can be considered an acceptable option, particularly in young children[1].

MSF would like to draw the attention of the Expert Committee to the following points:

- The efficacy of clavulanic acid against beta-lactamases is not dose-dependent: beta-lactamases are inhibited by low doses of clavulanic acid. Using the 7:1 ratio formulation allows 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 main advantage of the 7:1 ratio is that the required dose of amoxicillin is achieved without exceeding the maximum dose of clavulanic acid per day (10-15 mg/kg/day without exceeding 375 mg/day). If this maximum dose is exceeded, the risk of toxic effects –diarrhoea which may be severe – is increased. This warning pediatric consideration related to this adverse effect is especially relevant in MSF contexts, with limited resources for diagnosis and treatment, for all children suffering from the diseases above-listed.
- The 7:1 ratio formulations allow a twice-daily intake, reducing the burden for caregivers, while the 4:1 ratio formulations require a thrice-daily intake (every 8 hours).
- The two formulations of powders for oral suspension (4:1 ratio) currently included in the EMLc present the disadvantage of requiring clean water and measuring device for precise reconstitution then a refrigerated storage (between 2 and 8°C for 7 days), which can be not feasible in all contexts, particularly in low- and middle-income countries (LMICs). Moreover, the shelf life of powders for oral suspension is short (2 years). The dispersible tablet presents the advantage of an easier transport and storage than powder for oral suspension.
- In the treatment of infections in children, access to an amoxicillin + clavulanic acid 7:1 ratio formulation as child-friendly dispersible tablet is essential to increase ease and safety of administration and to improve tolerance, compliance, therefore allowing a better adherence to treatment.
- An 8:1 ratio dosage form should also be included in the EMLs, in order to ease supply in all settings. MSF has been using the powder for oral suspension with an 8:1 ratio and the

[1] The WHO AWaRe (Access, Watch, Reserve) antibiotic book [Internet]. https://www.who.int/publications-detail-redirect/9789240062382

dispersible tablet with a 7:1 ratio in its programs, respectively since 2013 and 2018, reserving the 4:1 ratio for multidrug resistant tuberculosis programs only (for use in combination with meropenem or imipenem + cilastatin).

- According to the application the (200 mg + 28.5 mg) amoxicillin + clavulanic acid dispersible tablet formulation is not currently available in any markets. It has regulatory approval in Malawi with submissions made to Regulatory authorities pending approval for Kenya, Rwanda and Uganda.
- The inclusion of a (200 mg + 28.5 mg) amoxicillin + clavulanic acid dispersible tablet in the EMLc will serve as a basis for National Essential Medicines lists and therefore will attract additional manufacturers, facilitate importations, alert manufacturers about the need for local registrations, will better allow for competition between manufacturers in order to reduce price and improve accessibility, particularly in LMICS, and will increase interest for child-friendly formulations.
- Previously, all products listed in the WHO Model List of Essential Medicines for Children were also listed in the WHO Model List of Essential Medicines: if this logic is maintained, (200 mg + 28.5 mg) amoxicillin + clavulanic acid dispersible tablet should also be added in the WHO Model List of Essential Medicines.

In light of all these elements, MSF urges the 24th Expert Committee on the Selection and Use of Essential Medicines to include (200 mg + 28.5 mg) amoxicillin + clavulanic acid dispersible tablet in the Core List of Section 6.2.1 “Access group antibiotics” in both the WHO Model List of Essential Medicines and the WHO Model List of Essential Medicines for Children.

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