F.1	Amoxicillin + clavulanic acid – dispersible tablet 200 mg + 28.5 mg – EMLc
Draft recommendation	☒ Recommended ☐ Not recommended Justification: Compared to other formulations of Amoxicillin + clavulanic acid already included in the EMLc this is a dispersible table with a 7:1 ratio. These characteristics have several advantages over a powder for reconstitution with 4:1 ratio. • Additional stability (it doesn't require cold storage) • Does not require to be reconstituted using a precise volume of water. • Due to higher ratio, it can be dosed Q12h (compatible with AWaRE approach recommendations) • It has been associated with lower frequency of adverse events. This formulation is already included in the EML.
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Multiple indications as for Amoxicillin + clavulanic acid 4:1 already included: • Powder for oral suspension: 125 mg (as trihydrate) + 31.25 mg (as potassium salt)/5 mL • Powder for oral suspension: 250 mg (as trihydrate) + 62.5 mg (as potassium salt)/5mL This formulation also addressed the lack of appropriate formulations for children. Global Accelerator for Paediatric Formulations (GAP-f) was created in response to this problem, their statement prioritizes the development of dispersible tablets over syrups and enabling formulary consolidation with flexible dosage forms. This formulation meets both criteria.

Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: Therapeutic equivalence between 7:1 and 4:1 ratio has been established (1). FDA and EMA consider both formulations as clinically equivalents. The 7:1 ratio has additional benefits: • Treatment of intermediate resistant pneumococci: - This formulation allows to administer higher doses of Amoxicillin without significantly increasing the proportion of clavulanic acid compared to the 4:1 formulation. - RCT, Schrag 2001, showed that high dose/ short course in respiratory infections led to significantly lower carriage rate compared to the low-dose long course. It also decreased the risk of TMP-SMX nonsusceptibility (2) • Higher adherence: -Studies have shown clear relationship between the number of daily doses and compliance. This was also seen in trial specifically Amoxicillin and clavulanic acid (3-7) - This was also seen in Schrag 2001(2) -Unfortunately a SR that evaluated the use of Amoxicillin +/- clavulanic acid did not show a difference in compliance between BID and TID (7)
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: Lower rates of adverse events have been reported in the 7:1 ratio formulation due to the lower proportion of clavulanic acid (8). A systematic review evaluating BID and TID regimens did not show statistically significant difference in the development of adverse reactions in general, diarrhea or dermatological events. Based on this we can conclude that the 7:1 formulation is at least as safe as the 4:1 formulation
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments: Same concerns as previously reported for the 4:1 formulation

Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☐ Yes ☒ No ☐ Not applicable Comments: Same requirements as previously reported for the 4:1 formulation
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☐ Yes ☒ No ☐ Not applicable Comments: There is no comparative data on the cost effectiveness of amoxicillin/clavulanic acid 4:1 ratio versus 7:1 ratio.
Are there any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable Comments: It is important to highlight that Amoxicillin/clavulanate 200mg/28.5 mg dispersible tablet is not currently available in any market
Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☒ Yes ☐ No ☐ Not applicable Comments: Compatible with AWaRE approach recommendations

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