C.1	Amitriptyline – removal of square box – EML
Draft recommendation	☒ Recommended ☐ Not recommended Justification: The reviewer recommends the removal of square box currently associated with Amitriptyline for the treatment of depressive disorder, considering the lack of comparative evidence on individual TCA medicines other than Amitriptyline and Clomipramine, and that Clomipramine proved to be less acceptable not only than Amitriptyline but also than placebo.
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Removing the square box can improve treatment outcomes based on evidence available for Amitriptyline and lack of evidence on other individual TCAs besides Clomipramine.
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: The review found that both amitriptyline (standardized mean difference [SMD]: -0.48; 95% CI: -0.55 to -0.41) and clomipramine (SMD: -0.33; 95% CI:-0.45 to -0.21) were more effective than placebo in terms of overall depressive symptoms reduction (i.e. efficacy outcome). However, the estimate for clomipramine was indirect, meaning that no studies comparing clomipramine with placebo were included. The only study comparing clomipramine with placebo, which randomized 38 participants only, did not include efficacy data suitable for re-analysis. Moreover, in terms of acceptability clomipramine was found to be the only medicine, among the 21 considered for the review, to be less acceptable than placebo.
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: No safety evidence or information was included in this application, as it is only for the removal of the square box.
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☐ No ☒ Not applicable Comments:

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:
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☐ Yes ☒ No ☐ Not applicable Comments:
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: The medicine is already registered in many countries and this application is only for the removal of the square box.
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: