R.2	EML Secretariat proposal to amend square box listings on the EML and EMLc
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: The WHO Model List has the potential to facilitate rational prescribing informed by evidence and enable better value procurement through tendering and competition leading to lower costs for individuals and health systems and improved access. It may help countries to define national lists and determine the alternatives that can be considered therapeutically equivalent. Providing more explicit information on therapeutically equivalent medicines within the square box listings on the Model List can solve uncertainties, better informing and supporting national decision-making (Cappello 2020). However, there is considerable heterogeneity in the way square box listing has been implemented since its introduction (1983). A revision to improve the Model List internal consistency is needed and could be of benefit for its correct implementation in the National medicine lists.
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	This Application has two fundamental objectives: **1**. **The identification and correction of heterogeneity, inconsistency, and undefinition in the application of the square box symbol through the Model List.** The EML Secretariat reviewed the 2019 Model List in order to identify groups of medicines/indications listed with a square box. They identified eight groups of which seven require revisions. The first three groups only require re-organization of existing information. Group 1: Listed medicines **without** a square box but with an asterisk denoting accepted alternatives. The proposal is to convert the asterisk into **qualified square box** listings to increase the clearness and homogeneity. This Reviewer agrees with the proposals by the Secretariat. Importantly, a few entries use the asterisk to explain that biosimilars can be used instead of the original compounds. This suggests that the general use of biosimilars (situations, conditions, characteristics, evidence, etc.) could be clearly defined. Standard criteria to accept biosimilars and statements valid for any biological product and its biosimilars would avoid the need to specify it in each case. The same was done with generic medicines in the case of small molecules in the past. Group 2: Listed medicines without a square box but with an asterisk denoting accepted alternatives. The proposal is to list the proposed alternatives independently. This Reviewer agrees with the proposals by the Secretariat. Group 3: Unrestricted square box listings where accepted alternatives are described in the Technical Report of the meeting where the listing was recommended. The proposal is to convert to **qualified square box** listings. This Reviewer agrees with the proposals by the Secretariat. The next groups (4 and 5) refer to the abandonment of "**unrestricted square box**" that is a source of confusion in the Model List. The revision of these groups requires

	judgment and, in some cases, assessment of evidence supporting the therapeutic comparability of each medicine and its alternatives. Group 4: Unrestricted square box listings where the Secretariat proposes specific alternatives for **qualified square box** listings. This group contains 20 medicines. This Reviewer agrees with the proposals by the Secretariat with a possible exception: Prednisone for ophthalmological inflammation (ATC Code: S01BA04). I would recommend moving this entry to Group 7 as the acceptable alternative options are not fully defined. A review of suitable alternatives should be undertaken, along with others in Group 7. Group 5: Unrestricted square box listing where alternatives can be defined by pharmacological class at the ATC4 level. This group contains 12 medicines. This Reviewer agrees with the Proposals by the Secretariat. Group 6: Unrestricted square box listing where the Secretariat proposes removal of the square box due to the absence of suitable alternatives. This group contains eight medicines. This Reviewer agrees with the Proposals by the Secretariat with a single exception: It is not clear to me the reason behind the proposal of replacing the square box of prostaglandin E (patency of the ductus arteriosus) with separate listings for prostaglandin E1 and prostaglandin E2. In the list currently "Prostaglandin E" is the listed medicine, "Prostaglandin E1" and "Prostaglandin E2" are mentioned as alternative formulations. Maybe a better option is to keep the square box but assign it to either E1 or E2 and specify the other as an alternative. Another possible option is to move it to Group 7 if a review is needed. Group 7: Unrestricted square box listings proposed for review of suitable alternatives. This group contains 23 medicines and – in the opinion of this Reviewer - should also include Prednisone (see comment on Group 4). For each of them a thorough assessment of the evidence supporting the interchangeability with alternative options should be done. Group 8: Qualified square box listings for which no amendments are proposed. No actions needed. **2. The definition and promotion of a common nomenclature to identify therapeutic options available for a single indication, which show minimal differences in either efficacy, safety or both, and thus, which could be prescribed indistinctly.** The Applicant uses the term "therapeutic equivalent" to refer to a different chemical structure from the original, but with a similar expected therapeutic effect and safety profile. However, "therapeutic equivalent" may have different meanings in different context, thus other terms are proposed, such as "suitable therapeutic alternatives, therapeutic alternatives, akin therapeutics", etc. For instance, according to the FDA Orange Book "approved drug products are considered to be therapeutic equivalents if they are pharmaceutical equivalents for which bioequivalence has been demonstrated, and they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labelling" (FDA Orange Book Preface 2021). Whatever the name, each and all the following conditions are required to allow considering a therapeutic equivalent:

	1. Approved for the same indications of use. 2. Have similar pharmacological effects - similar chemical structure, same pharmacologic group, or same biochemical - activity or therapeutic effect. 3. Have equivalent therapeutic efficacy and safety shown in clinical trials. In addition to the previous three requirements, pharmacokinetics, dosage, administration patterns, starting and ending conditions for the treatment, are considered to establish a safe interchange. The Application also considers the issue of applicability of square box listings to biologic and biosimilar medicines.
Have all important studies and all relevant evidence been included in the application?	☐ Yes ☐ No ☒ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included:
Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☐ Yes ☐ No ☒ Not applicable Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s). Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☐ Yes ☐ No ☒ Not applicable Comments:
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☐ No ☒ Not applicable Comments:
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Not applicable

Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Not applicable
Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☐ Yes ☐ No ☒ Not applicable Comments:
Are you aware of 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:
Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☐ No ☒ Not applicable Comments:
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	Not applicable
Any additional comments	None
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	**1. The identification and correction of heterogeneity, inconsistency, and undefinition in the application of the square box symbol through the Model List.** This Reviewer agrees with the proposed plan for a detailed revision of the application of the square box symbol. This Reviewer would like to propose a review of suitable alternatives in the case of • prednisolone (ophthalmological inflammation) rather than an automatic change to qualified square box; • prostaglandin E (patency of the ductus arteriosus) rather than the removal of square box. The identification and correction of heterogeneity, inconsistency, and undefinition that are frequent in the current version of the Model List would represent a big step to improve the applicability of the tool. **2. The definition and promotion of a common nomenclature to identify therapeutic options available for a single indication, which show minimal differences in either efficacy, safety or both, and thus, which could be prescribed indistinctly.** The promotion of a common nomenclature would also improve the applicability of the Model List. Moreover, it can encourage substitution by choosing an alternative with the best cost-effectiveness, thus containing health expenditure.

	A clear indication from the Expert Committee may help the revision by the EML Secretariat. This Reviewer is of the opinion that the use of "therapeutic equivalent" may not be optimal, given that its meaning in the context of the Model List is different from that of commonly applied in other systems (i.e., FDA Orange book). The square box concept applies to a variety of situations and, in majority of them, bioequivalence among the alternatives has not been demonstrated but extrapolated or assumed considering the molecular structure and other pharmacological characteristics. The term "therapeutic alternatives" may be a suitable option: in the absence of a demonstration of clinically meaningful differences, the "alternatives" listed with a square box are assumed to provide a similar therapeutic effect and safety profile. Thus, they should be perceived as possible options with decisions driven by other factors, e.g., costs and affordability. Regarding biologic and biosimilar medicines, this Reviewer believes that the inclusion of quality-assured biosimilars together with the originator should be the norm. Possible exceptions to this scenario should be documented with a clear demonstration that clinical meaningful differences exist. This Reviewer strongly support the proposal of having a common statement to be used for biosimilar throughout the Model List. Two scenarios are possible: - the application of the square box with a clear statement that the originator and their biosimilars (available at the time of the inclusion and afterwards) are "therapeutic alternatives" by default. - avoid the use of the square box (as for generic drugs) to minimise any possible false perceptions that the originator and their biosimilars differ but can, however, be considered "therapeutic alternatives" from a clinical perspective. The issues and barriers to interchangeability of biologic medicines to improve their access and affordability will be discussed by the Expert Committee in the context of three applications regarding the switch between originators and biosimilars of anti-TNF agents, insulins, and epoetins.
References (if required)	Cappello B, Moja L, Figueres A, Magrini N. The "Square Box": Therapeutic Equivalence as a Foundation of the WHO Model List of Essential Medicines. Front. Pharmacol. 2020. 11:578000. doi: 10.3389/fphar.2020.578000 FDA Orange Book Preface 2021 https://www.fda.gov/drugs/development-approval-process-drugs/orange-book-preface#_ftn5