

INFORMATION FOR APPLICANTS PREPARING A SUBMISSION FOR THE 2023 MEETING OF THE WHO EXPERT COMMITTEE ON SELECTION AND USE OF ESSENTIAL MEDICINES

Essential Medicines List Secretariat

DEPARTMENT OF HEALTH PRODUCTS POLICY AND STANDARDS



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Preface

The 24th meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines to revise and update the WHO Model List of Essential Medicines (EML) and Model List of Essential Medicines for Children (EMLc), will take place in April 2023.

This document describes the requirements for information to be included in submissions for inclusion of new medicines, for inclusion of new indications of currently listed medicines, and deletion of currently listed medicines for consideration by the Expert Committee.

For submissions relating to the inclusion or deletion of individual dosage form(s) and/or strength(s) of currently listed medicines for existing indications, please contact the EML Secretariat for further information.

During the submission period, the EML Secretariat is available to provide information and support to applicants, to ensure submissions adequately address the submission requirements. Final submissions must be emailed to the EML Secretariat (emlsecretariat@who.int) in both PDF and Word formats by **16 December 2022, 18:00 UTC**.

Please direct all enquiries to:

The Secretary
WHO Expert Committee on Selection and Use of Essential Medicines
Essential Medicines Team
Department of Health Products Policy and Standards
World Health Organization, Geneva
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- All submissions accepted for consideration by the Expert Committee will be published on the WHO website and should not include information that is commercial in confidence.
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Information to be included in submissions for inclusion or deletion of a medicine in the WHO Model Lists of Essential Medicines

1. TITLE PAGE

All submissions must have a title page describing the purpose of the submission and include the name and contact information of the individual(s) and/or organization(s) responsible.

2. SUMMARY STATEMENT OF THE PROPOSAL FOR INCLUSION, CHANGE OR DELETION

For **inclusions** of new medicines or new indications for currently listed medicines, briefly describe the proposal in terms of clinical indication(s), target population(s) and role in therapy for the requested medicine(s).

For **deletion** of medicines or indications, briefly describe the rationale and justification for the proposed deletion.

In all cases, specify whether the proposal relates to listing on the EML and/or EMLc, the core or complementary list, and of an individual medicine or as a representative of a pharmacological class or therapeutic group ("square box listing" – in which case the therapeutic alternatives should also be specified). For an explanation of the different terms, see below.

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- The Essential Medicines List for Children (EMLc) is intended for use for children up to and including 12 years of age.
 - The core list presents a list of minimum medicine needs for a basic healthcare system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.
 - The complementary list presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt, medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost-effectiveness in a variety of settings.
 - A "square box" symbol (□) is intended to indicate therapeutic alternatives to the listed medicine that may be considered for selection in national essential medicines lists. Alternatives may be individual medicines, or multiple medicines within a pharmacological class or chemical subgroup, defined at the 4th level of the [Anatomical Therapeutic Chemical \(ATC\) classification](#), which have similar clinical effectiveness and safety. The listed medicine should be the example of the class or subgroup for which there is the best evidence for effectiveness and safety. A square box is not used to indicate alternative generic brands of the same small molecule medicines, nor alternative biosimilars of biological medicines.
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Summary statement examples (illustrative purpose only):

This submission advocates the inclusion of daratumumab as an individual medicine in the complementary list of the EML for the treatment of adult patients with newly diagnosed and relapsed or refractory multiple myeloma in transplant and non-transplant settings.

Results of the evidence syntheses indicate that adding daratumumab to standard combination regimens probably leads to clinically important gain of overall survival, yet a higher number of people experiencing adverse events or serious adverse events. Evidence further suggests that more people receiving daratumumab may have a clinically important gain of quality of life, than people not receiving daratumumab.

Multiple myeloma is the second most common haematological malignancy with a global incidence of approximately 140,000 and an age-standardized incidence rate of 2.1 per 100,000 population in 2016. Since 1990, the incidence rate increased by 126% worldwide.



This submission is made in support of the inclusion of calcipotriol on the core list of the EML and EMLc, for the treatment of plaque type psoriasis in adults and children. This proposal is being made because there are currently no topical alternatives to the use of topical corticosteroids for the treatment of psoriasis included on the Model Lists. Listing is proposed for calcipotriol as the representative of topical vitamin D analogues, with therapeutic alternatives limited to calcitriol and tacalcitol.

Psoriasis is increasingly recognized as a disabling skin disease and has a worldwide distribution. Effective treatment of patients with mild to moderate plaque type psoriasis with calcipotriol has been reported in different clinical environments and in different age groups. Inclusion of calcipotriol on the Model Lists for the proposed indication would widen access to appropriate medications for the treatment of psoriasis and provide an effective alternative for the many patients with mild to moderate forms of this chronic condition who comprise the majority of cases.



This submission proposes the deletion of saquinavir (solid oral dosage form, 200 mg) from the core list of the EML as a treatment for HIV infection in adults.

Clinical use of saquinavir has declined substantially in recent years due to the development and availability of other EML-listed protease inhibitors for HIV that are associated with equal or greater effectiveness and a lower pill burden. Furthermore, saquinavir is no longer included in WHO HIV treatment guidelines as a preferred protease inhibitor for use in antiretroviral treatment regimens.

3. CONSULTATION WITH WHO TECHNICAL DEPARTMENTS

Applicants are encouraged to consult with relevant WHO technical departments as part of the submission preparation process.

Submissions received that have not been made by or in collaboration with WHO technical departments will be forwarded to the relevant technical department(s) for review and comment.

For submissions made following consultation with and support from the relevant WHO technical department, the name of the technical department and focal point(s) consulted should be included.

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- Note that WHO may not have a relevant technical department for all therapeutic areas. In such situations, applicants should consult the EML Secretariat.
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4. OTHER ORGANIZATION(S) CONSULTED AND/OR SUPPORTING THE SUBMISSION

The submission should indicate any other organization(s) that have been consulted in relation to the submission and/or support the submission. The affiliation between the applicant and the organization(s) should be specified.

Letters of support from such organizations should be included in an Annex to the submission.

5. KEY INFORMATION FOR THE PROPOSED MEDICINE(S)

International non-proprietary name (INN) of the proposed medicine(s)

Medicine(s) must be described using International Non-proprietary Names (INN) throughout the submission. INNs facilitate the identification of pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognised.

➤ A searchable database of INNs is available [here](#).

Anatomical therapeutic chemical (ATC) code of the proposed medicine(s)

The Anatomical Therapeutic Chemical (ATC) system classifies medicines according to the anatomical organ or system upon which they act and by therapeutic, pharmacological and chemical subgroups. A single medicine may have more than one ATC code, depending on the indications for use.

➤ A searchable version of the complete ATC index is available [here](#).

Dosage form(s) and strength(s) of the proposed medicine(s)

The submission must identify the specific dose forms(s) and strength(s) of the medicine(s) for inclusion or deletion.

If the proposal relates to medicines for inclusion on the EMLc, the submission must address availability of suitable, age-appropriate dosage forms and strengths for administration to infants and children up to 12 years of age.

Indication(s)

The indication(s) for which the medicine(s) is proposed for inclusion or deletion must be clearly specified. When available, the appropriate code for the proposed indication using the International Classification of Diseases, 11th Revision (ICD-11) must be included.

➤ A searchable database of ICD-11 codes is available [here](#).

6. PROPOSAL FOR AN INDIVIDUAL MEDICINE OR REPRESENTATIVE OF A PHARMACOLOGICAL CLASS / THERAPEUTIC GROUP.

The submission must indicate if the proposal relates to listing of an individual medicine or listing for one medicine as the representative of one or more therapeutic alternatives ("square box" listing).

A square box symbol (□) is used in the Model Lists to indicate that other medicines are acceptable therapeutic alternatives. The listed representative medicine should be the one for which there is the best evidence for effectiveness and safety. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources.

If listing is proposed for a medicine to be representative of a pharmacological class or therapeutic group, the specific alternative medicines should be specified (using INNs and ATC codes) and supporting evidence included.

➤ More information about the square box listing concept on the WHO Model Lists is available [here](#).

7. INFORMATION SUPPORTING THE PUBLIC HEALTH RELEVANCE

NEW MEDICINE(S) / INDICATION(S)

Submissions for inclusion of new medicine(s) and/or indication(s) must include information and evidence supporting the public health relevance of the proposed medicine(s), including:

- Epidemiological information on disease burden
- Target population(s)
- Alternative medicines currently included on the Model Lists for the proposed indication(s)

DELETIONS

Submissions for deletion of medicine(s) and/or indication(s) from the Model Lists must address any changes in public health need that may have arisen since the medicine was included in the Model Lists.

Submissions must identify any suitable alternative treatments available on the Model Lists and any foreseeable public health consequences of the proposed deletion.

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- The 2021 WHO Model List of Essential Medicines is available [here](#).
 - The 2021 WHO Model List of Essential Medicines for Children is available [here](#).
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8. TREATMENT DETAILS

Dosage regimen and duration of treatment

For inclusion of new medicines or new indications, the submission should describe the proposed therapeutic dosage regimen and duration of treatment for each medicine and indication. This should be informed by experimental, regulatory, and real-world data.

Requirements to ensure appropriate use of the medicine(s)

Consideration must be given to any additional requirements associated with appropriate use of the medicine, and avoidance of inappropriate use of the medicine(s); such as patient age and/or weight restrictions, diagnostic tests, specialized treatment facilities, administration requirements, monitoring requirements and skill levels of health care providers.

If companion *in vitro* diagnostic tests are required for appropriate use of the medicine(s), the submission must provide details of any such tests, with reference to their availability, and whether they are currently included on the WHO Model List of Essential In Vitro Diagnostics.

➤ The 2020 WHO Model List of Essential In Vitro Diagnostics is available [here](#).

Recommendations in existing WHO guidelines

Is the proposed medicine(s) recommended for use in current WHO guidelines? If yes, please provide summary details, including the strength of the recommendation and certainty of the evidence.

➤ A searchable repository of WHO guidelines is available [here](#).

Recommendations in other current clinical guidelines

Is the proposed medicine(s) recommended for use in other current clinical guidelines?

If yes, please provide details of the recommendation(s) and full reference to the guideline(s) concerned.

9. REVIEW OF BENEFITS: SUMMARY OF EVIDENCE OF COMPARATIVE EFFECTIVENESS

NEW MEDICINE(S) / INDICATION(S)

Submissions must include a summary of the available clinical evidence to support the comparative effectiveness of the proposed medicine(s) for the proposed indication(s).

Wherever possible, systematic reviews and meta-analyses should be presented. These may be from the published literature or conducted *de novo* by the applicant(s). When systematic reviews and meta-analyses are conducted by applicants for the purpose of the submission, this should be clearly indicated.

Evidence from individual randomized controlled trials can be presented showing patients characteristics, baseline risk for the main relevant outcomes in the standard treatment arm, absolute differences and measures of association.

Adequate consideration must be given to the quality of the studies (or risk of bias of individual study) together with comments on applicability/generalizability of the trial data (population, interventions, outcomes chosen), and on inconsistency among studies which may reduce the quality of the evidence.

Summaries of evidence from key trials using *Grading of Recommendations, Assessment, Development and Evaluation* (GRADE) tables should be included in the submission to support the comparative effectiveness and comparative safety of the proposed medicine(s).

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- More information regarding the GRADE approach for assessment of evidence quality and strength of recommendations is available [here](#). Software for producing GRADE tables can be downloaded [here](#).
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Systematic literature search

The submission must include information on the identification of clinical evidence using a systematic literature search (search strategy, search terms, inclusion and exclusion criteria, search results).

Summary of available evidence for comparative effectiveness

The submission should summarize the available data including an appraisal of quality of the evidence, outcome measures and results.

Include a summary of trial-based estimates of comparative effectiveness (including the number of participants and events; and measures of relative and absolute treatment effects). Preference must be given to comparisons with medicines already listed in the Model Lists or recognized standard(s) of care.

Assessment of applicability of the available evidence across diverse populations and settings

Evidence from a variety of clinical settings, including settings with different income levels and resources should be included, whenever available.

Submissions must evaluate evidence for both adults and children (when applicable to the proposed medicine), and for different patient populations (e.g. patients of different genders and ethnicities, pregnant and breastfeeding patients, elderly patients etc.) Where such evidence is not available, this should be clearly stated and the submission should present an assessment of the applicability of the available evidence to these different populations and settings.

DELETIONS

The submissions must present supporting evidence as justification for deletion of the medicine(s) and/or indication(s). with respect to any changes in clinical benefit that may have arisen since the medicine was included in the Model List.

10. REVIEW OF HARMS AND TOXICITY: SUMMARY OF EVIDENCE OF COMPARATIVE SAFETY

NEW MEDICINE(S) / INDICATION(S)

Submissions must include a summary of the available clinical evidence describing the safety of the proposed medicine(s) for the proposed indication(s).

Submissions should include the following:

- Estimates of total patient exposure to date
- Information on the identification of clinical evidence using a systematic literature search (search strategy, search terms, inclusion and exclusion criteria, search results).
- A summary of the available clinical evidence, including appraisal of quality and analysis of findings
- Descriptions of adverse effects of the proposed medicine(s) and estimates of their frequency and grading of severity
- A summary of comparative safety versus relevant comparators
- Consideration of the potential for and consequences of inappropriate use or use outside the proposed indication
- Information on any variation in safety that may relate to health systems or patient factors.
- Information on any warning or safety issues identified by regulatory authorities (e.g., black box warning, drug safety alerts etc).

DELETIONS

Submissions must present supporting evidence as justification for deletion of the medicine(s) and/or indication(s) with respect to any changes in safety that may have arisen since the medicine was included in the Model List.

11. SUMMARY OF AVAILABLE DATA ON COMPARATIVE COST AND COST-EFFECTIVENESS

NEW MEDICINE(S) / INDICATION(S)

The submission should include a summary of available data on the price of the medicine(s) in different markets, the estimated budget impact to patients and health systems, and data from economic analyses (e.g. cost-effectiveness, cost-utility studies) of the proposed medicine(s) versus other pharmacological or therapeutic interventions.

Data from cost-effectiveness and cost-utility analyses performed at national level should be included where available to provide general information on whether the intervention provides good value for money compared to alternative treatments already listed. The setting, willingness-to-pay threshold and the perspective from which the analyses were conducted should be clearly indicated.

The submission should consider the overall financial impact to health systems of making the medicine available.

Information on any special pricing arrangements, where they exist, should be included.

To justify the potential inclusion of medicines that incur greater costs to patients and health systems, the submission should clearly demonstrate the advantages of the proposed medicine relative to any currently listed medicines in key dimensions such as benefits, harms, compliance, ease of use, as an alternative for patients with allergies or other contraindications to already listed medicines, or non-responders to already listed medicines, etc.

DELETIONS

The submission must address any changes in cost / cost-effectiveness that may have arisen since the medicine was included in the Model List as justification for deletion of the medicine(s) and/or indication(s).

12. REGULATORY STATUS, MARKET AVAILABILITY AND PHARMACOPOIEAL STANDARDS

NEW MEDICINE(S) / INDICATION(S)

The submission must provide a summary of the regulatory status of the medicine(s) proposed and including the indication(s) for which the medicine(s) has regulatory approval.

Off-label indication(s) may be considered where off-label use is supported by evidence.

Regulatory status of the proposed medicine(s)

Submissions should include details of the regulatory status of the medicine(s) from national regulatory authorities.

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- Information regarding Stringent Regulatory Authorities (SRAs) and/or WHO-Listed Authorities (WLAs), including an interim list of National Regulatory Authorities, is available [here](#).
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Market availability of the proposed medicine(s)

The submission must provide information regarding the market availability of the medicine(s) in a variety of settings, including patent status and, where appropriate, any existing or planned licencing agreements with generic manufacturers and/or the Medicines Patent Pool.

Reference to existing or planned inclusion of the proposed medicine(s) on the WHO List of Prequalified Finished Pharmaceutical Products, should be included, where appropriate.

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- Information regarding finished pharmaceutical products and active pharmaceutical ingredients eligible for WHO Prequalification is available [here](#).
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Pharmacopoeial standards

The submission must indicate the availability of pharmacopoeial standards for the medicine(s) proposed in the British, European, International and United States Pharmacopoeias.

DELETIONS

The submission must address any changes in regulatory status (e.g. withdrawal of marketing authorization, new safety alerts) or market availability (e.g. product discontinuation by manufacturers) that may have arisen since the medicine was included in the Model List as justification for deletion of the medicine(s) and/or indication(s).

The submission must address potential implications of the proposed deletion in terms of access to alternative treatments, and include information on the market availability of alternative listed medicines for the same indication, including known shortages and/or supply-chain issues.

13. REFERENCES

The submission must be clearly referenced with in-text citations using Vancouver style.

Electronic reference library files must be exportable from the Word version of the submission document or provided separately.