World Health Organization

REGIONAL OFFICE FOR Europe

Consideration of cancer medicines as part of the revisions to 2019 WHO Model List of Essential Medicines for adults (EML) and Model List of Essential Medicines for children (EMLc)

Section 8

Immunomodulators and Antineoplastics

This summary has been prepared by the Health Technologies and Pharmaceuticals (HTP) programme at the WHO Regional Office for Europe.

It is intended to communicate changes to the 2019 WHO Model List of Essential Medicines for adults (EML) and Model List of Essential Medicines for children (EMLc) to national counterparts involved in the evidence-based selection of medicines for inclusion in national essential medicines lists (NEMLs), lists of medicines for inclusion in reimbursement programs, and medicine formularies for use in primary, secondary and tertiary care.

This document does not replace the full report of the WHO Expert Committee on Selection and Use of Essential Medicines (see The selection and use of essential medicines: report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2019 (including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2019 (WHO Technical Report Series, No. 1021). Licence: CC BY-NC-SA 3.0 IGO: https://apps.who.int/iris/bitstream/handle/10665/330668/9789241210300-eng.pdf?ua=1) and Corrigenda (March 2020) – TRS1021 (https://www.who.int/medicines/publications/essentialmedicines/TRS1021_corrigenda_March2020.pdf?ua=1).

Executive summary of the report: https://apps.who.int/iris/bitstream/handle/10665/325773/WHO-MVP-EMP-IAU-2019.05-eng.pdf?ua=1.

The revised lists of essential medicines are available here:

- World Health Organization Model List of Essential Medicines, 21st List, 2019. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO (https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?ua=1).

- World Health Organization Model List of Essential Medicines for Children, 7th List, 2019. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO (https://apps.who.int/iris/bitstream/handle/10665/325772/WHO-MVP-EMP-IAU-2019.07-eng.pdf?ua=1).

Address requests about publications of the WHO Regional Office for Europe to:
Publications
WHO Regional Office for Europe
UN City, Marmorvej 51
DK-2100 Copenhagen Ø, Denmark
Alternatively, complete an online request form for documentation, health information, or for permission to quote or translate, on the Regional Office website (http://www.euro.who.int/pubrequest).

Suggested citation. Consideration of cancer medicines as part of the revisions to 2019 WHO Model List of Essential Medicines for adults (EML) and Model List of Essential Medicines for children (EMLc), Section 8: Immunomodulators and Antineoplastics. Copenhagen: WHO Regional Office for Europe; 2020. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.
Sales, rights and licensing. To purchase WHO publications, see http://apps.who.int/bookorders. To submit requests for commercial use and queries on rights and licensing, see http://www.who.int/about/licensing.

may include recommendations on the use of medicinal products for an indication, in a dosage form, dose regimen, population or other use parameters that are not included in the approved labelling. Relevant stakeholders should familiarize themselves with applicable national legal and ethical requirements. WHO does not accept any liability for the procurement, distribution and/or administration of any product for any use.

EML CANCER MEDICINES WORKING GROUP (CMWG)

At the 2017 meeting of the WHO Expert Committee on Selection and Use of Essential Medicines, the potential to identify thresholds of benefits for cancer medicines was discussed. The Expert Committee recommended the establishment of the Cancer Medicines Working Group (CMWG) to review selected cancer medicines for the Essential Medicines List (EML - incorporating the Essential Medicines List for Children, EMLc). The aim was to establish clear principles that can guide the selection of optimal medicines to be considered for EML inclusion and review the available tools and thresholds for clinical and public health relevance of a medicine.

The mandate of this working group is to focus on the benefits and benefit-risk balance associated with new cancer treatments, and to discuss the magnitude of benefit issues, including the values of new treatments. It is important to be mindful of the risk of "selling hope" to patients, given the marginal benefits of some recently approved new medicines and also the consequences of the expenditure for patients and health systems.

The EML Cancer Medicines Working Group (CMWG) met in March 2018. The objectives of the CMWG meeting were to discuss:

- the magnitude of benefit of new cancer medicines approved in the last 15-20 years;
- recent trends in benefits of medicines approved by regulatory agencies;
- recent trends in how trials evaluating cancer medicines are designed;
- how to discriminate between medicines of marginal value and treatments that offer high value in terms of magnitude of clinical benefit and public health value, addressing both the curative and non-curative treatment settings.

A full report of the 22-23 March 2018 meeting of the CMWG has been published.[1] The Executive Summary of that report is reproduced here.

Executive Summary of report of CMWG meeting 22-23 March 2018

At the Seventieth World Health Assembly in 2017, World Health Organization (WHO) Member States adopted resolution WHA70.12, *Cancer prevention and control in the context of an integrated approach*, and WHO was requested to prepare a technical report on pricing approaches for cancer medicines for presentation to the Executive Board. A cancer medicines working group (CMWG) was convened by WHO in March 2018 at the recommendation of the WHO Expert Committee on the Selection and Use of

[1] World Health Organization. (2018). WHO EML cancer medicines working group (CMWG): report of the meeting 22-23 March 2018, Geneva, Switzerland. World Health Organization. https://apps.who.int/iris/handle/10665/272962. License: CC BY-NC-SA 3.0 IGO

Essential Medicines. The CMWG aims to obtain relevant input from experts to guide the selection of optimal cancer medicines under consideration for inclusion in the Essential Medicines List (EML).

- There was agreement on the usefulness and relevance of current magnitude of benefit scales for cancer medicines (ASCO-VF[2] and ESMO-MCBS[3]): these two scales have promoted the involvement of the oncology community (clinicians, researchers) and cancer patients in discussing the value of new cancer medicines and have fostered better understanding of what it is meant by relevant clinical benefit.

- The discussion on what is a clinically relevant magnitude of benefit was examined comparing ASCO-VF and ESMO-MCBS scales. Data from recent cancer trials were used to evaluate medicines recently approved by FDA (US Food and Drug Administration) and EMA (European Medicines Agency) using both scales: only a minority of newly approved medicines provide data on survival and quality of life. Indeed, clinically relevant data are often lacking at the registration phase.

- It was noted that for the vast majority (i.e. 75%) of cancer medicines approved over the last 15-20 years, there has been a lack of definitive evidence of substantial clinical benefit for patients at registration.

- The magnitude of benefit of treatment for OS (overall survival) and PFS (progression-free survival) might differ between one cancer and another (e.g. benefits that are relevant for chronic leukaemia might differ from benefits that are relevant for lung cancer). However, the CMWG agreed that an interval of overall survival benefits could be identified for consideration for inclusion of EML.

- The CMWG recommended WHO endorse the need to have overall survival as the main eligibility criterion of a medicine proposed for EML listing. Further the CMWG recommended endorsement of an interval for overall survival of at least 4-6 months for first-line treatments as a general guiding principle.

- Among the considerations that supported the 4-6 months overall survival interval were:

    - o a strong clinical and ethical conviction that for OS less than 3 months, the benefits seem weak, marginal or not relevant (depending on cancer types);

    - o a 3-month survival threshold has been endorsed by both ASCO and ESMO scales, with different implications in their respective scales;

    - o clinical trials estimates tend to overestimate the benefits because of patient selection, risk of bias and spurious findings. Patients included in clinical trials often differ from those seen in real life settings: benefits in patients seen in everyday practice might be less convincing as compared to those selected in trials. Trials often have important

[2] American Society of Clinical Oncology (ASCO) Value Framework

[3] European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale

methodological limitations, leading to biased estimates of intervention effectiveness. Single studies are often exposed to type I error. Finally, interventions studied in trials might not be directly transferable in LMICs as capacity of centers to deliver essential medicines and manage related toxicity might be diminished.

- In addition to the advantages of considering medicines for inclusion on the EML, endorsing a reference interval for clinical benefit will support countries in their local selection of cancer medicines most likely to have high impact without investing resources on treatments that provide little benefits.

- The CMWG recommended using the 4-6 month overall survival interval as a criterion for screening promising medicines proposed for EML listing. Medicines that have limited or no data on survival and are associated with highly relevant PFS/DFS (progression-free survival, disease-free survival) advantages could also be considered by the Expert Committee when these large benefits are validated and consistent across studies.

- The CMWG preferred the ESMO-MCBS to the ACSO-VF. The ESMO-MCBS allows for threshold values in relative and absolute gains. This is consistent with Expert Committee processes, where consideration is given to both relative and absolute effects by the Expert Committee in their evaluation of other medicines for inclusion on the EML.

- The CMWG recommended using the ESMO-MCBS as a screening tool to identify candidate medicines that might be potentially suitable for inclusion in EML. Since January 2016 ESMO - a non-governmental organization in official relations with WHO – has been evaluating all newly approved cancer medicines. This exercise was extended to some important previously approved medicines (e.g., trastuzumab). ESMO, in collaboration with the European Haematological Society, will expand the ESMO-MCBS to cover also haematological malignancies and treatments. Medicines that are top ranked by ESMO are strong candidates for evaluation by the EML Expert Committee. This means that WHO can focus its efforts on coordinating applications for top ESMO-MCBS scoring medicines, supporting tough decisions that countries are facing in terms of reimbursement. Applications for medicines that are not top-scoring would be still acceptable.

- The CMWG recommended that medicines that receive an ESMO score equal to 4, 5 or A-B could be eligible to become EML candidates if clinical benefits meet or exceed the 4-6 month survival interval. Among top-scoring medicines using the ESMO-MCBS there might be medicines that have still an uncertain risk to benefit profile since toxicity and therapy discontinuation are not fully considered by this scale. Candidates should always go through a standard application process and be fully examined by the EML Expert Committee.

- The CMWG emphasized the need to comprehensively evaluate all evidence, cumulating results across clinical trials and evaluating their consistency, to identify potential limitations of validity and generalizability at global level. The CMWG also advised to always give full consideration to toxicity data, treatment discontinuation, patient attrition, and selection of

settings and patients included in clinical trials as compared to low and middle-income settings and real-life populations.

- Ongoing work of the CMWG should involve the development of resource documents to inform and provide guidance to countries in the selection of cancer medicines at national level:

    1. A summary document of the current situations and trends in cancer medicine regulatory approvals with the recommendations of the CMWG on how to screen and select candidates for the WHO EML.

    2. A commissioned report showing the data on magnitude of benefit of all medicines registered in the last 15-20 years. The report will discuss the implications of using different scales to assess magnitude of benefit, the role of the WHO thresholds, and issues in evaluation clinical benefits. Finally, the report will give consideration to me-too drugs and biosimilars as important areas to expand access of cancer medicines to patients.

    3. A commissioned report outlining the historical trajectory of clinical trials in oncology (where they were first implemented 40 years ago) and how progressively the trial designs have been modified to better demonstrate small benefits in larger trials, satisfying the interests of commercial sponsors and regulatory agencies. Some additional considerations will be made on the importance of having public funded trials to support public health questions and fill important knowledge gaps.

2019 revisions to EML and EMLc

The 2019 WHO Expert Committee on Selection and Use of Essential Medicines acknowledged the work of the EML Cancer Medicines Working Group and endorsed the Working Group's recommendations that WHO adopt a threshold for benefit of at least 4-6 months survival gain to be considered as candidates for EML inclusion. The Committee acknowledged the role of the ESMO Magnitude of Clinical Benefit Scale[4] (ESMO–MCBS) as a screening tool to identify cancer treatments that have potential therapeutic value that warrants full evaluation for EML listing. Potential new EML cancer medicines, in general, should have a score on the ESMO-MCBS of A or B in the curative setting and of 4 or 5 in the non-curative setting. These scores would support a medicine being evaluated by the Expert Committee for inclusion in the EML through a full application.

The Committee recommended the continuation and further expansion of the activities of the Working Group. This should include the updated revision of treatment protocols for cancers previously considered by the Committee and identification of new cancer medicines that meet the above-mentioned criteria to be candidates for consideration of inclusion on the EML.

The Working Group should also review the issues being experienced at country level in relation to implementation of EML cancer medicine recommendations and access to cancer medicines. The Committee recommended the need for consolidation of cancer medicine recommendations and EML listings through a broader technical advisory group meeting, with country engagement to support implementation within a UHC perspective.

Section 8: Immunomodulators and antineoplastics

Table 1 provides a summary of changes made to Section 8.

Table 1 Considerations for changes to EML, EMLc

Section	Medicine	EML, EMLc
8.1	***Rejected*** glatiramer acetate (multiple sclerosis)	
	Rejected fingolimod (multiple sclerosis)	
	Rejected ocrelizumab (multiple sclerosis)	
8.1	***Anti-TNF biologics for chronic inflammatory conditions***	
	Adalimumab	EML, EMLc
	Listed with square box with nominated alternatives:	
	Etanercept, infliximab, certolizumab pegol and golimumab (adults)	EML
	Etanercept, infliximab (children)	EMLc
8.2	***Re-named Antineoplastic and supportive agents***	
	All-trans retinoid acid (Acute promyelocytic leukaemia)	EMLc

[4] https://www.esmo.org/score/cards

Section	Medicine	EML, EMLc
	Dasatinib (Imatinib-resistant chronic myeloid leukaemia)	EMLc
	Fluorouracil (nasopharyngeal carcinoma, early-stage colon cancer, early-stage rectal cancer, metastatic colorectal cancer)	EMLc
	Imatinib (chronic myeloid leukaemia, gastrointestinal stromal tumour)	EMLc
	Irinotecan (metastatic colorectal cancer)	EMLc
	Nilotinib (imatinib-resistant chronic myeloid leukaemia)	EMLc
	Oxaliplatin (early stage colon cancer, metastatic colorectal cancer)	EMLc
	Procarbazine (Hodgkin lymphoma)	EMLc
	Rituximab (diffuse large B-cell lymphoma)	EMLc
	Enoxaparin (anticoagulant) *Listed with a square box*	EMLc
	Extension of indications for currently listed cancer medicines for children Bleomycin (Kaposi sarcoma) Doxorubicin (Kaposi sarcoma) Vincristine (Kaposi sarcoma) Cisplatin (Nasopharyngeal carcinoma) Cyclophosphamide (Diffuse large B-cell lymphoma) Prednisolone (Diffuse large B-cell lymphoma) Cytarabine (Acute promyelocytic leukaemia) Daunorubicin (Acute promyelocytic leukaemia) Mercaptopurine (Acute promyelocytic leukaemia) Methotrexate (Acute promyelocytic leukaemia) Cytarabine (Acute myelogenous leukaemia) Hydroxycarbamide (Chronic myeloid leukaemia)	EMLc
	Rejected zoledronic acid	
	Arsenic trioxide (IV formulations; acute promyelocytic leukaemia)	EML, EMLc
	Realgar-Indigo naturalis (containing tetra-arsenic tetra-sulfide 30mg; acute promyelocytic leukaemia)	EML, EMLc
	Extension of indications for currently listed cancer medicines Cisplatin (cervical cancer) Carboplatin (cervical cancer) Paclitaxel (cervical cancer)	EML
	Rejected Fluorouracil (cervical cancer)	
	Pegaspargase (acute lymphoblastic leukaemia)	EML, EMLc
	Rejected pertuzumab (HER-2 positive breast cancer)	
	Rejected subcutaneous formulation of rituximab (diffuse large B-cell lymphoma, chronic lymphocytic leukaemia and follicular lymphoma)	
	Rejected subcutaneous formulation of trastuzumab (HER-2 positive breast cancer)	

Section	Medicine	EML, EMLc
	Rejected trastuzumab emtansine (HER-2 positive breast cancer)	
	Erlotinib (EGFR mutation positive advanced non-small cell lung cancer) *Listed with square box with nominated alternatives:* afatinib, gefitinib	EML
	Bortezomib (multiple myeloma)	EML
	Lenalidomide (multiple myeloma)	EML
	Thalidomide (multiple myeloma)	EML
	Melphalan (multiple myeloma)	EML
	Additional indication cyclophosphamide (multiple myeloma)	
	Additional indication doxorubicin (multiple myeloma)	
	Additional indication prednisone (multiple myeloma)	
	Additional indication dexamethasone (multiple myeloma)	
	Nivolumab (metastatic melanoma). *Listed with square box with nominated alternative:* pembrolizumab	EML
	Rejected atezolizumab (metastatic non-small cell lung cancer)	
	Rejected nivolumab (metastatic non-small cell lung cancer)	
	Rejected pembrolizumab (metastatic non-small cell lung cancer)	
	Abiraterone (metastatic castration-resistant prostate cancer)	EML
	Rejected Enzalutamide (metastatic castration-resistant prostate cancer)	

Decisions taken by Expert Committee in 2019

Medicines for multiple sclerosis – <u>rejected</u> application – EML and EMLc

Glatiramer acetate (ATC Code L03AX13) Fingolimod (ATC Code L04AA27) Ocrelizumab (ATC Code L04AA36)
REJECTED APPLICATION: The Expert Committee acknowledged the important public health burden of MS and the need for effective and affordable treatments and noted the large number of supporting letters that were received in relation to the application. The Committee appreciated the approach taken in the application to propose a limited number of essential medicines for MS but noted that the superiority of the presented medicines over other therapeutic options in terms of benefits, harms and affordability did not clearly emerge. The Committee noted that some commonly used treatments were not included (e.g. azathioprine, natalizumab, dimethyl fumarate, cladrabine) or were not given full consideration (rituximab) and the reasons for their exclusion were not clear. The Committee also noted ongoing development in international MS guidelines and would welcome a revised application for EML inclusion in the future which considers the relative roles of all available medicines for MS.

In particular, the Committee noted the evidence presented in the application in relation to rituximab. The Committee agreed that rituximab could have a relevant clinical role in treatment of MS and recommended that any future application should include evidence for rituximab versus active comparators, not just placebo.

The Committee, therefore did not recommend the addition of glatiramer acetate, fingolimod and ocrelizumab to the Model Lists at this time, and would welcome a revised application which comprehensively reviews the relative roles of relevant available medicines for MS.

TNF-alfa inhibitors for chronic inflammatory diseases – addition – EML and EMLc

Etanercept (ATC Code L04AB01) Infliximab (ATC Code L04AB02) Adalimumab (ATC Code L04AB04) Certolizumab pegol (ATC Code L04AB05) Golimumab (ATC Code L04AB06)
NEW MEDICINE ADDED: The Committee recognized that these auto-immune disorders are highly debilitating and that there is a public health need for effective treatments for patients who do not respond adequately to first-line treatments (e.g. methotrexate). The Expert Committee recommended the addition of adalimumab with a square box to the complementary list of the EML and EMLc for the second-line treatment of severe chronic inflammatory autoimmune disorders (rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and Crohn disease) on the basis of the positive benefit to harm profile of these medicines. For adult patients, therapeutically equivalent alternatives to adalimumab are limited to etanercept, infliximab, certolizumab pegol and golimumab. For children, therapeutically equivalent alternatives should be limited to etanercept and infliximab. The Committee also recognized that these medicines are associated with a significant budget impact to health systems. However, the availability of several therapeutically equivalent alternatives and the increasing availability of biosimilar products could lead to more market competition. The Committee recognized a potential expansion of the role of the Medicines Patent Pool (MPP) to biological medicines such as these as an opportunity to facilitate affordable access. Quality assured available biosimilars of these medicines should also be considered as therapeutically equivalent for procurement purposes. The Expert Committee recommended that WHO take action to facilitate access to these medicines through the WHO pre-qualification programme, and through collaboration with partners such as the Medicines Patent Pool.

8.2 Antineoplastics and supportive medicines

Cancer medicines for children

New medicines to be added to the EMLc – extending adult indications to children	
Medicine	**Paediatric indication(s)**
All-trans retinoic acid (ATRA)	Acute promyelocytic leukaemia
Dasatinib	Imatinib-resistant chronic myeloid leukaemia
Fluorouracil	Nasopharyngeal carcinoma Early-stage colon cancer Early-stage rectal cancer Metastatic colorectal cancer
Enoxaparin (*with a square box*)	For use as anticoagulant
Hydroxycarbamide	Chronic myeloid leukaemia
Imatinib	Chronic myeloid leukaemia Gastrointestinal stromal tumour
Irinotecan	Metastatic colorectal cancer
Nilotinib	Imatinib-resistant chronic myeloid leukaemia
Oxaliplatin	Early stage colon cancer Metastatic colorectal cancer
Procarbazine	Hodgkin lymphoma
Rituximab	Diffuse large B-cell lymphoma
REJECTED Zoledronic acid	Malignancy-related bone disease
Extension of indications for currently listed medicines	
Medicine	**Indication**
Bleomycin	Kaposi sarcoma
Doxorubicin	Kaposi sarcoma
Vincristine	Kaposi sarcoma
Cisplatin	Nasopharyngeal cancer
Cyclophosphamide	Diffuse large B-cell lymphoma
Prednisolone	Diffuse large B-cell lymphoma
Cytarabine	Acute promyelocytic leukaemia
Daunorubicin	Acute promyelocytic leukaemia
Mercaptopurine	Acute promyelocytic leukaemia
Methotrexate	Acute promyelocytic leukaemia
Cytarabine	Acute myelogenous leukaemia
Hydroxycarbamide	Chronic myeloid leukemia
NEW MEDICINE ADDED: The Expert Committee recommended the addition to the complementary list of the EMLc of ATRA, dasatinib, fluorouracil, imatinib, irinotecan, nilotinib, oxaliplatin, procarbazine and rituximab for the paediatric cancer indications outlined.	

NEW INDICATION: The Committee also recommended the extension of the current listings on the EMLc of bleomycin, doxorubicin, vincristine, cisplatin, cyclophosphamide, prednisolone, cytarabine, daunorubicin, mercaptopurine, methotrexate, cytarabine and hydroxycarbamide to include the indications outlined.

NEW MEDICINE ADDED: The Committee also recommended the addition to the core list of the EMLc of enoxaparin *with a square box* for use as an anticoagulant in children.

REJECTED APPLICATION: The Expert Committee did not recommend the addition of zoledronic acid to the complementary list of the EMLc for the treatment of malignancy-related bone disease. The Committee noted that data for its use in children are scant and fragmented. The Committee was also concerned that the effects of zoledronic acid in some paediatric cancers (e.g. osteosarcoma) were largely negative, and that there are insufficient long-term safety data of bisphosphonate use in paediatric cancer patients to be reassured of an acceptable benefit to harm ratio.

Furthermore, the Committee noted that although use of bisphosphonates in paediatric patients has been reported to be well tolerated, the impact of use in the context of patients with actively growing skeleton is not yet fully known.

Medicines for children with cancer – text clarifications

The application requested amendments to the text of the listings for a number of medicines and cancer indications on the EMLc:

1. Include alternate common names for some currently listed cancer medicines;
2. Include alternate common names for some listed indications;
3. Revised diagnosis terminology for germ cell tumours;
4. Alignment and addition of formulations;
5. Inclusion of variant formulations of listed medicines;
6. Addition of usage and supportive indications.

Following consideration of the proposals in the application, the Expert Committee made the following recommendations:

1. The additional alternate common names for medicines should not be added to the Model Lists. The current listings refer to the international non-proprietary names (INN) of the medicines. INN is the preferred nomenclature for medicines on the Model Lists.
2. The indication terminology for acute myelogenous leukaemia and Wilms tumour should be amended as proposed, as this would be consistent with ICD-11 terminology for these indications.
3. The indication of “malignant germ cell tumour” should not replace the indications of ovarian and testicular germ cell tumour as the Committee has not reviewed evidence for use of the relevant medicines in the treatment of germ cell tumours other than ovarian and testicular. Extending the indication to all germ cell tumours would require a full application.

4. With regard to formulation amendments, the Committee recommended that formulations of dexamethasone should be consistently listed across different sections of the list. The Committee also recommended that proposed new strengths of existing dose forms of calcium folinate, cyclophosphamide, etoposide should be added. However, the Committee did not recommend listing of the new dose forms for these medicines, and for mercaptopurine and methotrexate.
5. The Committee did not recommend the separate listing of prednisone with prednisolone, noting that the square box listing of prednisolone should be interpreted as including prednisone as an alternative. The Committee did not recommend the listing of etoposide phosphate as a variant of etoposide, as it considered that a full application would be appropriate to consider the clinical place of this medicine as an alternative to etoposide. The Committee also did not recommend listing for topical lidocaine + prilocaine, again considering that a full application would be required for this new combination product.
6. The Committee recommended including the indication "tumour lysis syndrome" with the listing for allopurinol. The Committee did not recommend including the other proposed supportive care indications with the listings of calcium folinate and mesna. Nor did the Committee recommend the proposed cautionary text for methotrexate and vincristine. The Committee acknowledged the critical importance of these messages but considered that this text was better suited for clinical practice guidelines, medication safety information and product packaging than on the Model Lists. The Committee did not recommend the proposed cautionary text about codeine with the listing for morphine. The Committee noted that codeine is not listed on the EMLc, and that alternatives to morphine are specified in the current listing as being limited to hydromorphone and oxycodone.

Arsenic therapies – addition – EML and EMLc

Arsenic trioxide (ATC Code L01XX27) Realgar-Indigo naturalis formula (RIF) (ATC Code: N/A)
The Committee endorsed the recommendations of the Cancer Medicine Working Group with regard to the proposed threshold of four to six months of overall survival benefit as a guiding principle for prioritizing cancer medicines for inclusion on the EML and applied this principle to the consideration arsenic-containing regimens for APML. **NEW MEDICINE ADDED:** The Expert Committee recommended the addition of arsenic therapies (intravenous arsenic trioxide and oral realgar-Indigo naturalis formulation) to the complementary list of the EML and EMLc for use in combination with all-trans-retinoic acid (ATRA) for treatment of patients with acute promyelocytic leukaemia, both newly diagnosed and relapsed. **NEW MEDICINE ADDED AND EXTENDED LISTINGS:** In consideration of a separate application of cancer medicines for children, the Committee also recommended the addition of ATRA to the EMLc, and extending the listings on the EMLc of cytarabine, daunorubicin, mercaptopurine, and methotrexate to include APML.

The Committee noted that treatment with ATRA plus arsenic was associated with high response rates and significant improvements in event-free and overall survival compared to ATRA plus chemotherapy and has a more favourable toxicity profile.

Medicines for cervical cancer – new indication – EML

Cisplatin (ATC Code L01XA01)
Carboplatin (ATC Code L01XA02)
Paclitaxel (ATC Code L01CD01)
REJECTED Fluorouracil (ATC Code L01BC02)

EXTENDED LISTINGS: The Expert Committee recommended extending the indications for cisplatin, carboplatin and paclitaxel on the complementary list of the EML to include treatment of invasive cervical cancer. The Committee considered that the evidence presented demonstrated these medicines to be associated with relevant survival benefits for patients. The Committee noted that regimens including these medicines are considered standard care in the curative and non-curative settings for cervical cancer.

Cisplatin is currently listed for use in the curative setting as a radiosensitizer and its listing is recommended to be extended to include the non-curative setting. Carboplatin is recommended for listing both in the curative and non-curative settings, and paclitaxel is recommended for listing in the non-curative setting.

REJECTED APPLICATION: The Expert Committee did not recommend extending the indications for fluorouracil to include treatment of cervical cancer in the curative setting. The Committee noted that when combined with radiotherapy, fluorouracil alone or in combination with cisplatin, was not associated with additional benefit compared to radiotherapy alone or cisplatin plus radiotherapy.

Pegaspargase – addition – EML and EMLc (ATC Code L01XX24)

NEW MEDICINE ADDED: The Expert Committee recommended the addition of pegaspargase to the complementary list of the EML and EMLc for use in the treatment of acute lymphoblastic leukaemia. The listing should indicate that quality-assured biosimilars of pegaspargase should also be considered as essential.

The Committee noted pegaspargase was associated with less immunogenicity and development of neutralizing antibodies than native asparaginase, which may offer advantages in terms of improved patient adherence enabling completion of treatment, thereby reducing the risk of relapse.

Pertuzumab – rejected application – EML (ATC Code L01XC13)

REJECTED APPLICATION: The Committee endorsed the recommendations of the EML Cancer Medicine Working Group with regard to the proposed threshold of four to six months of overall

survival benefit as a guiding principle for prioritizing cancer medicines for inclusion on the EML and applied this principle to the consideration of pertuzumab.

The Committee acknowledged that pertuzumab was associated with a relevant survival benefit, well beyond the established threshold, as first-line treatment of metastatic breast cancer, based on the results reported in the CLEOPATRA trial. However, the Committee expressed reservations about the generalizability of CLEOPATRA results in metastatic breast cancer and consistency of the clinical effectiveness of pertuzumab among studies both in early and metastatic breast cancer. These reservations are expanded below.

The Committee noted that only approximately 10% of patients in CLEOPATRA had received trastuzumab in the adjuvant or neoadjuvant setting. The Committee was concerned that the observed survival gains may not therefore be generalizable to patients with metastatic disease who have received prior adjuvant or neoadjuvant trastuzumab, making the magnitude of benefit in this population sub-group uncertain. The Committee also noted the results reported in the MARIANNE trial, where pertuzumab in combination with T-DM1 was not shown to have greater clinical benefit compared to trastuzumab plus chemotherapy or T-DM1 alone. The Committee was unable to reconcile the differences in the outcomes reported in the MARIANNE and CLEOPATRA trials.

The Committee also noted that the relevant survival gains observed in CLEOPATRA for metastatic breast cancer were not replicated in trials of pertuzumab in early stage breast cancer. The Committee accepted that trial results suggest pertuzumab offers a small incremental overall and disease-free survival benefit compared to placebo, based on an analysis at around 3 years median follow-up. The Committee considered that continued follow up was important to assess long-term overall survival but thought it unlikely that the magnitude of benefit would be greater with longer follow-up, given that anti-HER2 treatments are typically associated with a reduction in early recurrences, followed by a plateau effect.

The Expert Committee therefore did not recommend the addition of pertuzumab to the complementary list of the Model List for the treatment of early stage and metastatic HER-2 positive breast cancer. The Committee considered that the available evidence did not demonstrate a clinically meaningful survival benefit in early stage disease, and that there was important uncertainty surrounding the estimated magnitude of survival benefit in metastatic disease, with results seen in CLEOPATRA not replicated in other trials.

It was Committee's view that questions associated with differences in results from the CLEOPATRA and MARIANNE trials should be resolved by integration of the raw, individual patient trial data and independent re-analysis following a set of pre-planned hypotheses. The Committee recommended that WHO considers requesting access to the raw clinical trial data from CLEOPATRA and MARIANNE from the applicant, for an independent re-analysis arranged by WHO, and present the report of any such independent re-analysis, to the 2021 Expert Committee for consideration.

Rituximab – rejected application for new formulation – EML (ATC Code L01XC02)

REJECTED APPLICATION: The Expert Committee did not recommend the addition of new sub-cutaneous injection formulations of rituximab to the complementary list of the EML for use in the treatment of diffuse large B-cell lymphoma, chronic lymphocytic leukaemia and follicular lymphoma.

The Expert Committee acknowledged the potential benefits of the sub-cutaneous formulation over the listed intravenous formulation. However, with the availability of biosimilar versions of intravenous rituximab, the Committee was concerned that listing of the sub-cutaneous formulation, for which biosimilars are not yet available, could limit competition and therefore limit access for patients.

To help improve access, the Expert Committee recommended the current listing for intravenous rituximab on the EML should indicate that quality-assured biosimilars of rituximab should also be considered as essential medicines. In addition, the Expert Committee recommended that WHO continue to facilitate access to biosimilars through the Prequalification programme and WHO Collaborative Registration Procedure.

Trastuzumab – rejected application for new formulation – EML (ATC Code L01XC03)

REJECTED APPLICATION: The Committee did not recommend the addition of new sub-cutaneous injection formulations of trastuzumab to the complementary list of the EML for use in the treatment of early stage and metastatic HER-2 positive breast cancer.

The Expert Committee acknowledged the potential benefits of the sub-cutaneous formulation over the listed intravenous formulation. However, with the availability of biosimilar versions of intravenous trastuzumab, the Committee was concerned that listing of the sub-cutaneous formulation, for which biosimilars are not yet available, could limit competition and therefore limit access for patients.

To help improve access, the Expert Committee recommended the current listing for intravenous trastuzumab on the EML should indicate that quality-assured biosimilars of trastuzumab can also be considered as essential medicines. In addition, the Expert Committee recommended that WHO continue to facilitate access to biosimilars through the Pre-Qualification programme and WHO Collaborative Registration Procedure.

Trastuzumab emtansine (T-DM1) – rejected application for addition – EML (ATC Code L01XC14)

REJECTED APPLICATION: The Committee endorsed the recommendations of the EML Cancer Medicine Working Group with regard to the proposed threshold of four to six months of overall survival benefit as a guiding principle for prioritizing cancer medicines for inclusion on the EML and applied this principle to the consideration of trastuzumab emtansine. The Committee acknowledged that for second line treatment of metastatic breast cancer, trastuzumab emtansine was associated

with a relevant survival benefit, within the range of the established threshold. However, the Committee noted that survival benefits did not meet the 4-6 month threshold when trastuzumab emtansine was used as first line treatment in the metastatic setting, or in early stage breast cancer.

Existing EML-listed options are available for metastatic disease and may be suitable alternatives (e.g., trastuzumab, taxanes, etc.). However, the Committee noted the current challenges in achieving full access to trastuzumab in many settings. Taking this into account, trastuzumab emtansine for second-line treatment of metastatic disease (i.e. late in the care pathway) was considered to be a lower priority for EML inclusion at this time.

Compared to the 2017 application, the Committee noted that few new clinical data were included in the current application and that the request was not based on a comprehensive review encompassing additional breast cancer medicines, compared with the standard of care, which would allow countries to understand the additional value of adding each option to national EMLs.

The Expert Committee therefore did not recommend the addition of trastuzumab emtansine to the complementary list of the EML for the treatment of unresectable locally advanced and metastatic HER-2 positive breast cancer.

Tyrosine-kinase inhibitors for non-small cell lung cancer – addition – EML

Afatinib (ATC Code L01XE13) Erlotinib (ATC Code: L01XE03) Gefitinib (ATC Code: L01XE02)
NEW MEDICINE ADDED: The Committee endorsed the recommendations of the EML Cancer Medicine Working Group with regard to the proposed threshold of four to six months of overall survival benefit as a guiding principle for prioritizing cancer medicines for inclusion on the EML and applied this principle to the consideration of the tyrosine kinase inhibitors afatinib, erlotinib and gefitinib. The Committee noted that afatinib, erlotinib and gefitinib were all scored as 4/5 on the ESMO-MCBS v1.1 for this indication. The Expert Committee recommended the addition of erlotinib with a square box to the complementary list of the EML for first-line treatment of EGFR mutation positive advanced non-small cell lung cancer. Afatinib and gefitinib should be considered as therapeutically equivalent alternatives. The Committee noted that these medicines are associated with relevant survival benefits for patients, acceptable toxicity and improvements in quality of life compared to chemotherapy. The Committee also noted that since these medicines were considered for inclusion on the EML in 2015, generic versions of these medicines are more widely available, as are quality-assured diagnostic molecular tests for EGFR mutations.

Medicines for multiple myeloma – addition – EML

Bortezomib (ATC Code L01XX32) Lenalidomide (ATC Code L01AX04) Thalidomide (ATC Code L04AX02)
The Committee acknowledged the treatment of MM to be complex and recognized the need to provide the best available care within the context of both non-transplant and transplant settings. **NEW MEDICINE ADDED:** The Expert Committee recommended the addition of bortezomib, lenalidomide and thalidomide to the complementary list of the EML for the treatment of multiple myeloma patients in both non-transplant and transplant eligible/available settings, on the basis of good evidence showing large improvement in survival outcomes with acceptable safety for patients with newly-diagnosed multiple myeloma. With regard to MM treatment in transplant-eligible populations, the Committee noted the additional evidence presented as part of the review process supporting standard regimens used in the induction phase before ASCT involving three-drug combinations: VTD (bortezomib, thalidomide, dexamethasone), VCD (bortezomib, cyclophosphamide, dexamethasone), PAD (bortezomib, doxorubicin, dexamethasone) and RVD (lenalidomide, bortezomib, dexamethasone); and of the benefit of lenalidomide maintenance therapy following ASCT. **NEW MEDICINE ADDED and ADDITIONAL INDICATION:** In the non-transplant setting, the Committee acknowledged that the proposed medicines are administered as part of treatment regimens involving companion cytotoxic agents and/or steroids (melphalan, cyclophosphamide, prednisone, dexamethasone). Accordingly, the Committee recommended the addition of melphalan to the complementary list of the EML for treatment of multiple myeloma, and that the current listings for cyclophosphamide, doxorubicin, prednisone and dexamethasone be extended to include multiple myeloma as an indication.

Anti PD-1 / PD-L1 Immune checkpoint inhibitors – application for addition – EML and EMLc

Atezolizumab (ATC Code L01XC32) Nivolumab (ATC Code L01XC17) Pembrolizumab (ATC Code L01XC18)
The Committee endorsed the recommendations of the EML Cancer Medicine Working Group with regard to the proposed threshold of four to six months of overall survival benefit as a guiding principle for prioritizing cancer medicines for inclusion on the EML and applied this principle to the consideration of the immune checkpoint inhibitors. **NEW MEDICINE ADDED:** The Committee noted that there were no treatment options for metastatic melanoma currently included on the Model List. The Committee recommended the addition of nivolumab and pembrolizumab to the complementary list of the EML, for use as front-line monotherapy for treatment of patients with unresectable and metastatic melanoma on the basis of evidence of significantly increased overall survival for patients that met the recommended threshold

for benefit, and in the absence of other EML-listed treatment options. Listing should be for nivolumab with a square box indicating pembrolizumab as a therapeutically equivalent alternative. The Committee noted that nivolumab was scored as 4/5 on the ESMO-MCBS v1.1 for this indication.

The Committee considered that more mature data would be necessary before listing of these medicines could be considered for use in adjuvant indications of radically resected melanoma.

REJECTED APPLICATION: The Committee did not recommend listing of atezolizumab, nivolumab or pembrolizumab for treatment of patients with metastatic NSCLC at this time, as the Committee considered that their precise place in the treatment/immunotherapy of this condition is still evolving. The Committee noted the evidence of efficacy in the treatment of patients with metastatic NSCLC with these agents. The Committee observed that the duration of follow-up of the single studies for frontline and second line immunotherapy in trials for lung cancer was generally shorter than three years and considered that data from longer follow-up would better capture the actual magnitude of benefit. By the time of the next Expert Committee meeting in 2021, more mature data will be available for metastatic NSCLC and also for use of these agents in locally advanced non-resectable disease, and as adjuvant therapy.

Furthermore, the Committee noted that the landscape of clinical development of cancer immunotherapy still has some areas of uncertainty with regard to the optimal time for introduction of treatment (front-line or second line), appropriate patient selection, and whether or not use of ICIs in combination with other medicines is superior.

The Expert Committee expressed concern about the potential budget impact of oncology medicines which could be an impediment to access, and countries may not be able to list these medicines on their national EMLs. Therefore, the Committee recommended that WHO engage stakeholders to find ways to facilitate better access and affordability as a high priority through avenues such as the Medicines Patent Pool, WHO prequalification and collaborative registration procedures. The Committee also recommended ongoing activities of the EML Cancer Medicines Working Group to include identification of obstacles to access and affordability of cancer medicines, and pricing data collection.

Medicines for prostate cancer – EML

Abiraterone (ATC Code: L02BX03) Enzalutamide (ATC Code: L02BB04)
The Committee endorsed the recommendations of the EML Cancer Medicine Working Group with regard to the proposed threshold of four to six months of overall survival benefit as a guiding principle for prioritizing cancer medicines for inclusion on the EML and applied this principle to the consideration of abiraterone and enzalutamide. **NEW MEDICINE ADDED**: The Expert Committee recommended the addition of abiraterone to the complementary list of the EML for use in the treatment of metastatic castration-resistant prostate cancer.

The Expert Committee acknowledged the significant public health burden of prostate cancer, which afflicts an increasing number of people in all countries, irrespective of income. The Committee recalled that the EML currently includes docetaxel, bicalutamide and leuprorelin for use in the treatment of metastatic prostate cancer. However, a significant proportion of patients will not respond to these medicines and patients will ultimately develop resistance.

The Committee noted that abiraterone and enzalutamide have each been shown to be effective treatments for metastatic castration-resistant prostate cancer, both in chemotherapy-naive and in pre-treated patients. The Committee noted that abiraterone had not shown any relevant clinical advantage over enzalutamide in terms of efficacy outcomes or safety. However, the Committee recognized the potential advantages offered by abiraterone in terms of emerging dosing strategies (lower doses may be possible when administered with food), reduced pill burden potentially improving adherence, wider availability of generics and potential associated cost savings.

REJECTED APPLICATION: Given that metastatic prostate cancer often requires treatment over longer periods of time (above 1 year) and that low dosing and availability of generics would be associated with substantial cost savings, the Committee decided not to recommend listing abiraterone with a square box indicating enzalutamide as an alternative. While enzalutamide remains an effective therapeutic option for mCRPC, its use instead of abiraterone could result in considerable additional expenditure at country level, without additional clinical benefit. The Committee considered that addition of abiraterone alone on the EML serves to support its use, promoting competition between brand and generic medicines, and improving access and affordability.

The WHO Regional Office for Europe

The World Health Organization (WHO) is a specialized agency of the United Nations created in 1948 with the primary responsibility for international health matters and public health. The WHO Regional Office for Europe is one of six regional offices throughout the world, each with its own programme geared to the particular health conditions of the countries it serves.

Member States

Albania
Andorra
Armenia
Austria
Azerbaijan
Belarus
Belgium
Bosnia and Herzegovina
Bulgaria
Croatia
Cyprus
Czechia
Denmark
Estonia
Finland
France
Georgia
Germany
Greece
Hungary
Iceland
Ireland
Israel
Italy
Kazakhstan
Kyrgyzstan
Latvia
Lithuania
Luxembourg
Malta
Monaco
Montenegro
Netherlands
North Macedonia
Norway
Poland
Portugal
Republic of Moldova
Romania
Russian Federation
San Marino
Serbia
Slovakia
Slovenia
Spain
Sweden
Switzerland
Tajikistan
Turkey
Turkmenistan
Ukraine
United Kingdom
Uzbekistan

World Health Organization
Regional Office for Europe

UN City, Marmorvej 51,
DK-2100 Copenhagen Ø, Denmark
Tel.: +45 45 33 70 00 Fax: +45 45 33 70 01
Email: eurocontact@who.int
Website: www.euro.who.int