medicines patent pool

Unitaid
Innovation in Global Health

PRIORITISATION OF MEDICINES FOR IN-LICENSING BY THE MEDICINES PATENT POOL – 2021

EXECUTIVE SUMMARY

TABLE OF CONTENTS

AKNOWLEDGEMENTS

The MPP is grateful to the experts participating in various meetings including the WHO Think Tank, the Paediatric Antiretroviral Drug Optimization (PADO), the Workshop of the Long-Acting/Extended Release Antiretroviral Resource Program (LEAP) and the Conference on Retroviruses and Opportunistic Infections (CROI) whose contributions and insights contributed to the updating of the MPP prioritisation. The MPP also acknowledges the WHO Essential Medicines List Expert Committee and the Cancer Medicines Working Group, As well as the International Diabetes Federation. Inputs from our Scientific Advisory Panel and Expert Advisory Group were invaluable to this process. Discussions over the past year with a wide range of experts in academic and civil society organizations were also extremely helpful to further understand the potential of different medicines. The final assessment, however, is the responsibility of the MPP alone.

1. INTRODUCTION

The mission of the Medicines Patent Pool (MPP) is to increase access to, and facilitate the development of, life-saving medicines for low- and middle-income countries (LMICs) through voluntary licensing and patent pooling. To do so, MPP identifies suitable candidates for in-licensing on an annual basis using a prioritization framework, to ensure MPP focuses its efforts on medicines for which licensing could have the greatest public health impact.

The prioritization methodologies used for HIV and HCV therapeutics were developed in 2016[1], with minor refinements in subsequent years[2,3], and was further adapted to tuberculosis in 2018. Later, a new prioritization framework was developed to assess medicines in other diseases areas that were on the WHO Model List of Essential Medicines (EML) or had strong potential for future inclusion on that list. MPP engaged in extensive expert consultations to devise a methodology that could be applied to different disease areas with very different characteristics. Assessments in HIV, TB and HCV continued to rely on the previous methodology. The present document seeks to harmonize the different methodologies to develop a single framework for prioritisation, and presents the results of MPP's prioritisation in 2021. The framework provides a set of key criteria to be assessed, while detailed sub-criteria are adapted to specific diseases as needed.

1.1 GENERAL PRINCIPLES AND UNDERLYING ASSUMPTIONS

In developing the harmonized prioritization framework, MPP was guided by a number of key principles. These were as follows:

- The methodology should draw from the existing methodologies being used by MPP for prioritisation of i) candidate medicines in HIV, hepatitis C and TB, and ii) candidate medicines for in-licensing under an MPP expanded mandate.
- It should result in the prioritisation of medicines for which an MPP intervention could yield the greatest impact on public health in LMICs.
- In its clinical assessment, where possible, MPP should rely on existing assessments by the World Health Organization (e.g., WHO treatment guidelines or the WHO Model List of Essential medicines (EML)) in order not to duplicate work and to align with established global health priorities.
- Where such WHO assessments are not available, MPP undertakes its own assessments relying on the available literature as well as on assessments made by other reputable public health institutions.[4]
- The methodology takes into account the multiple challenges to access that may affect the likelihood of an MPP licence resulting in public health impact, including those that an MPP intervention may have very limited capacity to influence (e.g., diagnostic capacity in LMICs, or health systems needs for administering the product).
- A product can be assessed using the harmonized framework once it has entered phase II clinical development. The exception for this are early-stage long-acting technology candidates which are often long-acting formulations of approved products. In assessing the relevance of prioritizing before they enter later stages of clinical development, we ensure that early and harmonized efforts are carried out to put access mechanisms in place as soon as indications of possible effectiveness are available. This is in line with the latest recommendations to support access to long-acting HIV prevention products, and where possible to facilitate further development[5].
- For candidates that are still in the development pipeline, and for which access plans are not known yet, availability and affordability of the products in LMICs cannot be assessed, but it is generally assumed that an MPP intervention could contribute to supporting broader access.
- The prioritisation framework is meant to be sufficiently flexible to be relevant across various health areas, with the possibility of adaptations to specific areas, where appropriate.

1 https://medicinespatentpool.org/fr/news-publications-post/mpp-prioritisation-reports/

2 https://medicinespatentpool.org/uploads/2020/04/2017-Prioritisation-Report-Prioritisation-of-HIV-and-Hepatitis-C-medicines-for-in-licensing-by-the-Medicines-Patent-Pool.pdf

3 https://medicinespatentpool.org/uploads/2020/04/2018-Prioritisation-Report.pdf

4 For example, the European Society of Medical Oncology's Magnitude of Clinical Benefit Scale (ESMO-MCBS) for medicines for cancer.

5 https://www.iavi.org/news-resources/features/evolving-access-pathways-for-long-acting-hiv-prevention-products.

In order to guide in-licensing candidates' prioritisation under the new framework, we have assessed the medicines by addressing three sequential questions:

1. **How important is a given medicine in LMICs?**
2. **Are there access challenges with respect to that medicine in LMICs?**
3. **Is the medicine patented in LMICs?**

These questions offer insights about three dimensions of the drug subject to prioritisation, that are summarized in table 1. Each dimension is further broken down into a series of considerations. This table is to be read as a forward pass, where items in each column need to be positively assessed in order to move on to the next column items. The results of the prioritisation are provided below for each therapeutic area. Note that the MPP does not include in its prioritisation medicines for which it has already obtained licences in the past[6].

TABLE 1. OVERVIEW OF MPP'S HARMONIZED PRIORITISATION FRAMEWORK

1: PUBLIC HEALTH & CLINICAL RELEVANCE *How important is this medicine in LMICs?*	2: ACCESS CHALLENGES *Are there access challenges in LMICs?*		3: PATENT STATUS IN LMICS *Is the medicine patented in LMICs?*
Assessment by WHO For medicines already assessed by WHO, MPP relies on WHO's assessment for public health and clinical relevance	**Access challenges where MPP intervention could have direct impact**	**Additional challenges that may impact on success of an MPP intervention**	**Years to patent expiry** Considers filed and granted compound patents and secondary patents
Public health relevance of disease • Burden of disease in LMICs • Burden of disease in specific populations • Burden of disease in HIV/TB • Availability of alternative Treatments	**Availability** Includes whether the product is registered and available in LMICs and whether it is available in the needed formulation	**Complexity/availability of diagnosis** Considers complexity of diagnosis and the extent to which diagnostic capacity is available in LMICs to identify patients that could benefit from the medicine	**Geographical coverage of patents** Focuses on low- and middle-income countries with special attention to patents in key countries of manufacture
Clinical relevance of the medicine • Safety and tolerability • Efficacy • Ease of administration and scale-up in resource limited settings • Special populations (children, other subpopulations) The assessment is made in comparison to the standard of care (SOC)	**Affordability** Includes affordability of drug in question and companion drugs	**Health systems and infrastructure needs** Looks at whether administration of the treatment is complex, whether it requires hospitalization, whether it requires specialists	
	Existing access programs Includes considerations such as coverage, accessibility and eligibility, and sustainability of the program	**Potential Market Size** Considers whether purchase of the product (or the product it would replace) is covered by government procurement or donor funding in LMICs	

6 MPP licences to date are for abacavir (paediatric), atazanavir, bictegravir, cobicistat, daclatasvir, dolutegravir, elvitegravir, emtricitabine, glecaprevir, lopinavir, pibrentasvir, raltegravir (paediatric), ravidasvir, ritonavir, sutezolid, tenofovir alafenamide, tenofovir disoproxil fumarate and several combinations containing these medicines. In addition, it has obtained a licence on patents that are relevant to darunavir and collaborated on commitments not to enforce patents for darunavir (paediatric) and nevirapine.

2. MPP PRIORITIZATION IN HIV

TABLE 2: MPP PRIORITIES IN HIV

PRODUCT *Originator(s)*	**SUMMARY OF ASSESSMENT**
Cabotegravir *(ViiV Healthcare)*	**Clinical Relevance** Cabotegravir is approved as 1-2 monthly intramuscular injectable co-packed with rilpivirine.[7] Cabotegravir is also available as a standalone injectable, thus removing the cold chain requirements associated with rilpivirine. These long-acting formulations could potentially increase adherence and ease pill burden in PLHIV. A lead-in of daily oral cabotegravir is required prior to initiation of the long-acting formulation. Studies have shown cabotegravir plus rilpivirine to be non-inferior to three-drug antiretroviral regimens[8,9]. In clinical trials, long-acting cabotegravir was also 89% more effective than daily oral FTC/TDF as PrEP,[10,11] potentially offering an important option for people at substantial HIV risk. This appears to be a particularly promising prevention tool for certain high-risk populations in LMICs. Cabotegravir is also being studied in pregnancy[12] and in children older than 12 years[13], but no results have been released so far. Cabotegravir is generally well tolerated with a promising safety profile. **Access** Access plans and prices in LMICs are not yet known. The market for PrEP is growing substantially (approximately 1 million people in 2020) and cabotegravir, if available at affordable prices, could be a strong candidate for inclusion in national HIV programs, particularly for PrEP. **Patent Status in LMICs** Compound patents filed or granted in several LMICs, expected expiry 2026. Patents on the long-acting parenteral composition filed or granted in several LMICs, expected expiry 2031.
Islatravir *(Merck Sharp and Dohme)*	**Clinical Relevance** Islatravir is being studied in combination with doravirine (more details below) for the treatment of HIV naïve patients[14] and in virologically suppressed patients.[15] Interim results showed that 90% of people treated with islatravir plus doravirine had undetectable HIV viral load at week 96, showing that the combination works at least as well as a three-drug regimen. Long-acting treatments combining islatravir (Merck) and lenacapavir (Gilead) are underway. Islatravir is also being studied in combination with doravirine in patients having at least triple-class resistance[16], representing a valuable opportunity for heavily treatment-experienced HIV patients, and studies are ongoing in paediatric populations.[17] Once-monthly oral islatravir is studied for PrEP in people at low risk of HIV[18], in high-risk cisgender women[19] and in men and transgender women who have sex with men[20]. Islatravir is generally well tolerated and has a promising safety profile. As clinical studies are ongoing, all products prioritized are subject to them proving safe and efficacious. **Access** Access plans and prices for LMICs are not yet known (still in clinical development). **Patent Status in LMICs** Patent applications on islatravir for the treatment or prophylaxis of HIV in a dosing regimen less frequent than once-daily expected expiring Patent applications on combinations containing islatravir, processes and implants containing islatravir, with expected expiry 2037 - 2040.

7 https://www.fda.gov/drugs/human-immunodeficiency-virus-hiv/fda-approves-cabenuva-and-vocabria-treatment-hiv-1-infection#:~:text=FDA%20Approves%20Cabenuva%20and%20Vocabria%20for%20the%20Treatment%20of%20HIV%2D1%20Infection,-Share&text=FDA%20approved%20CABENUVA%20(cabotegravir%20extended,co%2Dpackaged%20for%20intramuscular%20use.&text=oral%20therapy%20for%20patients%20who%20will%20miss%20planned%20injection%20dosing%20with%20CABENUVA.

8 https://clinicaltrials.gov/ct2/show/NCT02951052

9 https://clinicaltrials.gov/ct2/show/NCT02938520

10 https://clinicaltrials.gov/ct2/show/NCT02720094

11 https://clinicaltrials.gov/ct2/show/NCT03164564

12 https://clinicaltrials.gov/ct2/show/NCT04518228

13 https://clinicaltrials.gov/ct2/show/NCT03497676

14 https://clinicaltrials.gov/ct2/show/NCT04223778

15 https://clinicaltrials.gov/ct2/show/NCT04233879

16 https://clinicaltrials.gov/ct2/show/NCT04233216

17 https://clinicaltrials.gov/ct2/show/NCT04295772

18 https://clinicaltrials.gov/ct2/show/NCT04003103

19 https://clinicaltrials.gov/ct2/show/NCT04644029

20 https://clinicaltrials.gov/ct2/show/NCT04652700

PRODUCT *Originator(s)*	SUMMARY OF ASSESSMENT
Lenacapavir *(Gilead Sciences)*	**Clinical Relevance** Lenacapavir is being studied in combination with other ARVs for the treatment of ART naïve patients[21] as well as in heavily treatment-experienced HIV patients with multidrug resistance.[22] It is being studied as a daily oral formulation (200-900mg range), however, sub-cutaneous injection formulations (900mg) could provide longer bioavailability[23]. Low in vivo systemic clearance and slow-release kinetics from the subcutaneous injection site allows for 6-monthly lenacapavir administration[24]. Lenacapavir is also planned to be studied for PrEP in the form of 6-months, stand alone, sub-cutaneous injections, in comparison with TAF/FTC and TDF/FTC[25]. Lenacapavir is generally well tolerated and with a promising safety profile[26]. As clinical studies are ongoing, all products prioritized are subject to them proving safe and efficacious. **Access** Access plans and prices for LMICs are not yet known (still in clinical development). **Patent Status in LMICs** Several patents on lenacapavir have been filed or granted in LMICs expiring between 2034 and 2037.

3. MPP PRIORITIZATION IN TB

TABLE 3: MPP PRIORITIES IN TB

PRODUCT *Originator(s)*	SUMMARY OF ASSESSMENT
Bedaquiline *(Janssen)*	**Clinical Relevance** Bedaquiline is an FDA and EMA approved drug developed by Janssen for the treatment of multidrug resistant TB. Bedaquiline is also studied for drug-sensitive TB[27]. As per WHO guidelines[28], bedaquiline has been recommended as part of various regimens for MDR-TB. **Access** A new discounted price of USD 340 for the six months course of bedaquiline was announced with the Global Drug Facility in July 2020, with the possibility of further discounts based on volumes[29]. In 2020 the price was USD 272 for 135 LMICs. **Patent Status in LMICs** The compound patent on BDQ is expected to expire in 2023, with secondary patents expiring in 2025 and 2027. A license has been granted to one company for the manufacture and supply of BDQ in Russia and certain other countries in the EECA region.

In addition to bedaquiline, MPP also assessed two other tuberculosis medicines, both of which are currently recommended in WHO guidelines. For delamanid, the existence of an exclusive license means that there would not be a role for MPP in relation to that medicine. For pretomanid, the product was developed by a public health organization with extensive access plans for that molecule. In addition, there are no patents on the compound and remaining patents on combinations have already been licensed on a non-exclusive basis to at least three companies.

21 https://clinicaltrials.gov/ct2/show/NCT04143594
22 https://clinicaltrials.gov/ct2/show/NCT041500683
23 https://clinicaltrials.gov/ct2/show/NCT04143594
24 CROI2021 - LENACAPAVIR (GS-6207): FIRST CLINICALLY ACTIVE LONG-ACTING INHIBITOR OF HIV CAPSID
25 CROI2021 - LENACAPAVIR (GS-6207): FIRST CLINICALLY ACTIVE LONG-ACTING INHIBITOR OF HIV CAPSID
26 CROI2021- POTENT ANTIVIRAL ACTIVITY OF LENACAPAVIR IN PHASE 2/3 IN HEAVILY ART-EXPERIENCED PWH
27 https://clinicaltrials.gov/ct2/show/NCT03338621
28 https://www.who.int/tb/publications/2019/rapid_communications_MDR/en/
29 http://www.stoptb.org/news/stories/2020/ns20_024.html.

4. LONG-ACTING TECHNOLOGIES

In 2019, MPP initiated an exploratory evaluation, which concluded that MPP could play an important role in facilitating the development of, and access to, new long-acting (LA) formulations and technologies of potential importance in LMICs[30].

In addition to the technologies/formulations listed here, MPP has acquired in 2021 licences on two technologies: Long-acting injectable HIV candidate formulation based on DcNP technology (University of Washington) and Long-acting formulations for hepatitis C, TB and malaria treatment and/or prevention, based on Emulsion-Templated Freeze Drying (ETFD) technology (Tandem Nano Ltd. For the consortium led by the University of Liverpool). As such, they are excluded from this document.

TABLE 4. PRIORITY LONG-ACTING TECHNOLOGY/FORMULATION FOR IN-LICENSING

PRODUCT *Originator(s)*	**SUMMARY OF ASSESSMENT**
Long-acting ivermectin depot based on MedinCell's BEPO® technology[31] for malaria vector control *(MedinCell)*	Based on its BEPO® technology, MedinCell is developing a long-acting ivermectin injectable formulation for malaria vector control[32,33]. The formulation uses the BEPO technology to form a fully bioresorbable depot once injected subcutaneously. It would be administered once at the beginning of the malaria transmission season with an active duration of three months. Malaria vector mosquitoes are sensitive to ivermectin in the host bloodstream, as it reduces their fertility and survivorship or even induces their mortality[34]. Using ivermectin for vector control in humans to reduce malaria transmission is deemed to be safe and potentially an effective addition to the malaria elimination toolbox[35,36,37,38,39].

MPP is also approaching innovators working on platform technologies that could enable long-acting formulations of medicines for treatment and prevention of infectious diseases of special importance in LMICs. As many of these are in very early stages of development, data are not always available publicly to assess the relevance of including the candidate products as per the prioritization framework.

30 Global Health Panel: Opportunities to Address Global Health Challenges With Long-Acting Technologies, 3rd Long-acting injectables and implantables conference, LaJolla CA, Feb 6, 2020

31 https://www.medincell.com/bepo/

32 https://unitaid.org/project/long-acting-medicines-for-innovative-vector-control/#en

33 https://www.medincell.com/wp-content/uploads/2020/03/PR_MedinCell-Unitaid-EN_March2020.pdf

34 Mekuriaw W, Balkew M, Messenger LA, Yewhalaw D, Woyessa A, Massebo F. The effect of ivermectin on fertility, fecundity and mortality of Anopheles arabiensis fed on treated men in Ethiopia. Malar J. Published online 2019:1-10. doi:10.1186/s12936-019-2988-3

35 Chaccour C, Rabinovich NR. Ivermectin to reduce malaria transmission II . Considerations regarding clinical development pathway. Malar J. 2017;16(166):1-13. doi:10.1186/s12936-017-1802-3

36 Chaccour C, Hammann F, Rabinovich NR. Ivermectin to reduce malaria transmission I . Pharmacokinetic and pharmacodynamic considerations regarding efficacy and safety. Malar J. 2017;16(161). doi:10.1186/s12936-017-1801-4

37 Foy BD, Alout H, Seaman JA, et al. Efficacy and risk of harms of repeat ivermectin mass drug administrations for control of malaria (RIMDAMAL): a cluster-randomised trial. Lancet. 2019;393:1517-1526. doi:10.1016/S0140-6736(18)32321-3

38 Alout H, Foy B. Ivermectin: a complimentary weapon against the spread of malaria? Expert Rev Anti Infect Ther. 2018;15(3):231-240. doi:10.1080/14787210.2017.1271713

39 Slater HC, Foy BD, Kobylinski K, et al. Ivermectin as a novel complementary malaria control tool to reduce incidence and prevalence: a modelling study. Lancet Infect Dis. 2020;20(4):498-508. doi:10.1016/S1473-3099(19)30633-4

5. ESSENTIAL MEDICINES FOR NON-COMMUNICABLE DISEASES AND REPRODUCTIVE, MATERNAL, NEW-BORN AND CHILD HEALTH (RMNCH)

In 2018, MPP expanded its mandate to include essential medicines for non-communicable diseases, including medicines on the WHO Essential Medicines List (EML) and medicines with strong potential for inclusion on the EML. In 2021, the WHO Expert Committee updated the EML and considered in its assessments the comparative cost-effectiveness of submitted medicines and specifically called onto MPP to explore licensing possibilities for several drugs (both those included on the EML and those not included partly due to concerns on cost effectiveness, and partly due to insufficient/premature data). Consistent with MPP's current mandate, the selection only includes patented small molecules. An assessment is ongoing on the possible application of the MPP model to biotherapeutics, which may lead to the inclusion of patented biotherapeutics to MPP's priority list.

TABLE 5: MPP PRIORITIES IN CANCER

PRODUCT *Originator(s)*	**SUMMARY OF ASSESSMENT**
Osimertinib *(AstraZeneca)*	**Clinical Relevance** Osimertinib was submitted for inclusion in the EML for the first-line treatment of EGFR+ non-small cell lung cancer.[40] The Expert Committee acknowledged that CD4/6 inhibitors had potential for future inclusion and recommended that MPP explore the application of its licensing model to these medicines. Osimertinib proved to be effective in improving both progression-free and overall survival in non-small cell lung cancer compared to first and second generation TKIs with a comparable safety profile. (ESMO-MCBS Score= 4).[41,42] **Access** Availability/affordability of osimertinib in many LMICs remains limited. Access plans for osimertinib in LMICs are unknown. **Patent Status in LMICs** The primary patent on osimertinib is expected to expire in 2032, with secondary patents expiring in 2035.
Ribociclib *(Novartis)* Abemaciclib *(Eli Lilly)* Palbociclib *(Pfizer)*	**Clinical Relevance** CDK 4/6 inhibitors were submitted for inclusion in the EML for the treatment of: HR+/HER2- breast cancer.[43] The Expert Committee acknowledged that CD4/6 inhibitors had potential for future inclusion and recommended that MPP explore the application of its licensing model to these medicines. Studies have found significant advantage of CDK 4/6 inhibitors over endocrine therapy in first- [44,45] or second line[46] setting. The European Society of Medical Oncology (ESMO) recommend the use of CDK4/6 inhibitors in the first- line setting in patients with hormone receptor positive/ HER2-negative advanced/metastatic breast cancer (the most frequent stage at presentation in LMICs). The use of CDK4/6 inhibitors showed a significant improvement of survival and quality of life.[47] **Access** Current access programmes are limited to few LMICs,[48] with caps on the number of cycles supported, and may be limited to public hospitals.[49] Availability/affordability challenges in LMICs remain. **Patent Status in LMICs** Patents on all three CDK 4/6 inhibitors have been filed in several LMICs. The primary patent on palbociclib expires in 2023 with secondary patents expiring in 2034; for ribociclib primary patents expire in 2027-2029 with secondary patents expiring in 2031-2036; for abemaciclib primary patents expire in 2029.

40 https://cdn.who.int/media/docs/default-source/essential-medicines/2021-eml-expert-committee/applications-for-addition-of-new-medicines/a.23_osimertinib.pdf?sfvrsn=593530b5_4

41 https://cdn.who.int/media/docs/default-source/essential-medicines/2021-eml-expert-committee/applications-for-addition-of-new-medicines/a.23_osimertinib.pdf?sfvrsn=593530b5_4

42 https://www.annalsofoncology.org/article/S0923-7534(21)04007-2/fulltext

43 https://cdn.who.int/media/docs/default-source/essential-medicines/2021-eml-expert-committee/applications-for-addition-of-new-medicines/a.8_cdk-4-6-inhibitors.pdf?sfvrsn=bf85ebfa_4

44 https://oncologypro.esmo.org/meeting-resources/esmo-congress-2021/overall-survival-os-results-from-the-phase-iii-monaleesa-2-ml-2-trial-of-postmenopausal-patients-pts-with-hormone-receptor-positive-human-epi

45 https://oncologypro.esmo.org/meeting-resources/esmo-congress-2021/paloma-4-primary-results-from-a-phase-iii-trial-of-palbociclib-pal-letrozole-let-vs-placebo-pbo-let-in-asian-postmenopausal-women-with-e

46 https://oncologypro.esmo.org/meeting-resources/esmo-congress-2021/efficacy-and-safety-of-ribociclib-rib-in-combination-with-letrozole-let-in-patients-with-estrogen-receptor-positive-advanced-breast-cancer-abc

47 Yendala R, Thein K, Swarup S, et al. A Systematic Review and Meta- Analysis of Randomized Controlled Trials to Evaluate the Risk of Health-Related Quality of Life Events in Patients With Hormone Receptor-Positive HER2-Negative Metastatic Breast Cancer Treated With CDK 4/6 Inhibitors. Journal of the National Comprehensive Cancer Network. 2019. https://doi.org/10.6004/jnccn.2018.7234

48 https://accesstomedicinefoundation.org/media/uploads/downloads/613f5fb390319_Access_to_Medicine_Index_2021.pdf

49 https://accesstomedicinefoundation.org/media/uploads/downloads/613f5fb390319_Access_to_Medicine_Index_2021.pdf

PRODUCT *Originator(s)*	SUMMARY OF ASSESSMENT
Ibrutinib *(Pharmacyclics INC (AbbVie)/ Janssen)* Zanubrutinib *(Biegene)* Nilotinib *(Novartis)*	**Clinical Relevance** Ibrutinib is on the complementary list of the EML for the treatment of relapsed/refractory chronic lymphocytic leukaemia (with and without chromosome 17p deletion), based on evidence of a major sustained benefit in terms of overall survival and progression-free survival, less acute toxicity, and minimal risk of secondary leukaemias compared with chemo-immunotherapy.[50] Ibrutinib was also one of the drugs that the Expert Committee specifically called MPP to explore licensing possibilities for. Zanubrutinib was submitted for inclusion in the EML for the management of relapsed/refractory CLL, as well as relapsed/refractory mantle cell lymphoma. The Expert Committee did not recommend its inclusion in the 23rd edition, due to limited efficacy data, concerns on toxicity, and unlikely cost-effectiveness at the reported price. The expert committee recommended that MPP explore licensing possibilities for zanubrutinib. Zanubrutinib is a next-generation, highly potent, selective, Bruton tyrosine kinase (BTK) inhibitor, which has shown better safety and efficacy than first-generation BTK inhibitor with greater BTK selectivity and less off-target inhibition against alternative kinases (thus, fewer adverse effects). Nilotinib was included in the EML in 2017 for the treatment of imatinib-resistant chronic myeloid leukemia, and in the EMLc in 2019 for the same indication in pediatrics. Nilotinib shows superior performance to first generation BTK inhibitors both in the first line[51] and second line setting.[52] **Access** Nilotinib is part of the Max Foundation's access programs,[53] with Novartis donating nilotinib to 33 countries through Max Foundation.[54] Access/affordability challenges with all three drugs remain in several LMICs. **Patent Status in LMICs** The primary patent on ibrutinib expires in 2026 The primary patent on zanubrutinib expires in 2034 The primary patent on nilotinib expires in 2023
Enzalutamide *(Pfizer, Astellas)*	**Clinical Relevance** Enzalutamide has been included on the complementary list of the EML as a therapeutic alternative to abiraterone for treatment of metastatic castration-resistant prostate cancer and the WHO Expert Committee recommended that MPP explore licensing. Enzalutamide is indicated as first-line therapy for the treatment of patients with metastatic castration-resistant prostate cancer who have not received chemotherapy or who have previously received docetaxel and is also indicated for the treatment of non-metastatic castration-resistant prostate cancer. Enzalutamide demonstrates comparable efficacy to abiraterone, has a different mechanism of action and a different toxicity profile, and may be an option for patients unable to be treated with abiraterone. It can also be administered as monotherapy, reducing drug burden and toxicities to patients. **Access** Astellas' country teams provide a number of schemes to both payers and self-pay patients in a few countries, however these schemes are not standardized across countries, and it is not clear how many countries are included. **Patent Status in LMICs** The primary patent on the drug expires in 2027. At least one generic supplier, Glenmark, has entered the market.[55]

50 Executive Summary. The Selection and Use of Essential Medicines 2021. Report of the 23rd WHO Expert Committee on the Selection and Use of Essential Medicines. Virtual Meeting, 21 June – 2 July 2021. World Health Organization. Geneva. WHO/MHP/HPS/EML/2021.01

51 https://www.nejm.org/doi/full/10.1056/nejmoa0912614

52 https://pubmed.ncbi.nlm.nih.gov/29459949/

53 https://www.themaxfoundation.org/work/cancer-programs/

54 https://accesstomedicinefoundation.org/access-to-medicine-index/report-cards/novartis-ag#performance-breakdown

55 https://cdn.who.int/media/docs/default-source/essential-medicines/2021-eml-expert-committee/applications-for-addition-of-new-medicines/a.11_enzalutamide.pdf?sfvrsn=9a9e697d_4

TABLE 6: MPP PRIORITIES IN DIABETES

PRODUCT *Originator(s)*	**SUMMARY OF ASSESSMENT**
Empagliflozin *(Boehringer Ingelheim - BI)* Dapagliflozin *(AstraZeneca)* Canagliflozin *(Janssen)*	**Clinical Relevance** The SGLT2 inhibitors have been included on the core list of the EML as add-on treatment for adults with type 2 diabetes with or at high risk of cardiovascular disease and/or diabetic nephropathy. SGLT2i have been found to be effective in achieving glycemic control in non-pregnant adults.[56] Recent data has shown significant cardiovascular benefit[57] and renal benefits,[58] including in patients without diabetes. **Access** Current access programmes in LMIC are unclear. Access/affordability challenges remain for SGLT2 inhibitors in many LMICs. **Patent Status in LMICs** Primary patents on canagliflozin expire in 2024 with secondary patents expiring in 2027-2031; dapagliflozin patents expire in 2020-2023 (with secondary patents in 2027-2028); empagliflozin patents expire in 2025 (with secondary patents in 2026-2034).

TABLE 7. MPP PRIORITIES IN PREVENTION OF PPH

PRODUCT *Originator(s)*	**SUMMARY OF ASSESSMENT**
Heat-stable Carbetocin *(Ferring Pharmaceuticals)*	**Clinical Relevance** Carbetocin is included in the EML for Postpartum hemorrhage (PPH), and is recommended in the WHO Guidelines for the Prevention of Postpartum Hemorrhage to include the use of carbetocin (100 µg, IM/IV) for the prevention of PPH "for all births in contexts where its cost is comparable to other effective uterotonics"[59] noting that the current cost of using carbetocin for PPH prevention was greater than the cost of using other effective uterotonics. The heat-stable formulation of carbetocin does not require cold-chain transport and storage; it has been shown to maintain stability over a period of 36-48 months at 30°C and 75% relative humidity, and as such may offer significant benefits over oxytocin in contexts where cold chain cannot be guaranteed. **Access** Ferring has developed an access agreement to provide carbetocin in the public sector of low income and lower middle-income countries at a price that is comparable to the price UNFPA currently pays for quality-assured oxytocin).[60,61] This agreement, however, does not include upper middle-income countries nor private markets in these countries. **Patent Status in LMICs** While the primary patent on carbetocin has expired, there are patents granted or applications pending on the heat-stable formulation in several LMICs, expiring in 2031.

56 https://cdn.who.int/media/docs/default-source/essential-medicines/2021-eml-expert-committee/applications-for-addition-of-new-medicines/a.29_sglt2.pdf?sfvrsn=35f1e4c8_4

57 https://www.nejm.org/doi/full/10.1056/NEJMoa1911303

58 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6628616/

59 http://apps.who.int/iris/bitstream/handle/10665/277276/9789241550420-eng.pdf?ua=1&ua=1

60 Note that oxytocin that does not meet international quality standards can reach prices of around 10 to 15 cents

61 https://www.ferring.com/heat-stable-carbetocin-has-been-added-to-the-who-essential-medicines-list-for-the-prevention-of-excessive-bleeding-after-child-birth/#note3

medicines
patent
pool

Rue de Varembé 7
1202 Geneva, Switzerland

www.medicinespatentpool.org