medicines patent pool

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

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TABLE OF CONTENTS

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1. INTRODUCTION

The mission of the Medicines Patent Pool (MPP) is to facilitate the development of and increase access to, life-saving medicines for low- and middle-income countries (LMICs) through voluntary licensing and patent pooling. To do so, the first step for MPP is to identify suitable candidates for in-licensing using a prioritisation framework that is applied on an annual basis. This mechanism contributes to ensuring 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. Following MPP's mandate expansion in 2019[4], a new prioritisation 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. Later in 2021, MPP developed a harmonised framework to assess all products regardless of the disease area. The framework provides a set of key criteria to be assessed, while detailed sub-criteria are adapted to specific diseases, as needed. This framework streamlines MPP product assessment by combining elements from the previous methodologies.

The MPP prioritization framework is applied to all approved medicines or medicines in late-stage clinical development (at least in phase 2) that MPP may consider for in-licensing. The prioritisation process generates two outputs for each disease area, i) a priority list and ii) a watchlist. A product falls in the priority list if there are sufficient clinical data supporting its full assessment. To be prioritised, a product should also have a clear advantage compared to the standard of care (e.g., better tolerability, higher safety profile, easier administration route, higher efficacy, etc.). Additionally, a product is prioritised when MPP's model is fit for purpose and a clear impact on access in LMICs can be expected from an MPP intervention. Alternatively, a product falls into the watchlist when it appears to be promising but clinical development is still ongoing; therefore, the clinical advantage over standard of care or the significance of MPP model are still unclear or data are still lacking to assess whether an MPP intervention may have impact on access.

Early-stage long-acting products are so far excluded from this harmonised framework because there is as yet limited data on their safety and efficacy. The approach of the MPP in relation to such formulations and technologies is not only to support access to future products, but also to facilitate their further development. MPP has therefore developed a separate decision tree for taking decisions on the prioritisation for licensing of early-stage long-acting medicines, and some have already been licenced to MPP after being prioritised.

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 https://medicinespatentpool.org/uploads/2020/07/Prioritisation-Framework-MPP-New-Areas.pdf

2. PRIORITISATION FRAMEWORK

In order to guide in-licensing candidates' prioritisation under the 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 summarised 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.

TABLE 1. OVERVIEW OF MPP'S HARMONISED 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 and does not separately assess them for public health and clinical relevance **Assessment by other Public Health organization (e.g., ESMO)** Assessments by other public health organization other than WHO are used to inform MPP's further assessment of clinical and public health benefit	**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 LMICs 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(s)	**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	

The results of the prioritisation are provided below for each therapeutic area. The assessment will continue to be undertaken on an annual basis to re-assess priorities, in close collaboration with MPP's Scientific Advisory Panel, based on new clinical evidence, changes to WHO recommendations, changes in patent status, evolution in access programmes and changes in prices or market forecasts for medicines. It should be noted that the MPP does not include in its prioritisation medicines for which it has already obtained licences in the past[5].

5 MPP licences to date are for abacavir (paediatric), atazanavir, bictegravir, cobicistat, daclatasvir, dolutegravir, patents related to darunavir, elvitegravir, emtricitabine, lopinavir & ritonavir, molnupiravir, nirmatrelvir, glecaprevir/pibrentasvir, raltegravir (paediatric), ravidasvir, ritonavir, sutezolid, tenofovir alafenamide, tenofovir disoproxil fumarate and several combinations containing these medicines. MPP has also licences for early-stage long-acting products for HIV, hepatitis C, latent tuberculosis and malaria, as well as for technologies for SARS-CoV2 diagnostics and R&D for prevention tools and other diagnostic tools for SARS-CoV2.

3. MPP PRIORITISATION IN HIV

3.1 GRAPHICAL SUMMARY OF MPP PRIORITIES IN HIV

The table below provides a graphical summary of MPP priorities and watchlist respectively, in the field of HIV. Two HIV medicines (or investigational treatments/prevention tools) are identified as priorities and three are included in the watchlist. Among the priorities, cabotegravir has been included into MPP prioritization list since 2017, while lenacapavir was already identified in the 2021 prioritisation process as a promising investigational drug.

Dapivirine monthly ring and islatravir were prioritised in the MPP 2021 prioritisation report but were deprioritised in 2022. Dapivirine monthly ring was de-prioritised because its patent will expire in 2023, limiting considerably the impact of MPP licensing[6]. Islatravir was de-prioritised because of the recent concerns about decreased CD4+ cells counts in treated patients, which have led to clinical trials to be put on hold[7]. MPP acknowledges that long-acting antivirals could play an important role in HIV treatment and prevention, therefore MPP will keep monitoring the development of islatravir with the possibility of re-inclusion into its priority list in the future as relevant.

TABLE 2. SUMMARY TABLE FOR HIV

				EASE OF ADMINISTRATION			SAF
	SRA approval	New MoA	Number of years in MPP Priority List	Daily oral formulation	Long-acting formulation	Adherence	Side effects
MPP Priorities							
Cabotegravir	Yes	No	6	○	IM	●	○
Lenacapavir	No	Yes	2	○	SQ O	●	?
MPP Watchlist							
GSK3640254	No	Yes	NA	○	NA	○	?
Doravirine	Yes	No	NA	○	NA	○	○
Rilpivirine	Yes	No	NA	○	IM	●	●

6 https://www.medspal.org/?page=1
7 https://www.merck.com/news/merck-announces-clinical-holds-on-studies-evaluating-islatravir-for-the-treatment-and-prevention-of-hiv-1-infection/

PILLAR 1						PILLAR 2		PILLAR 3
ETY	EFFICACY		SPECIAL POPULATIONS			ACCESS CHALLENGES		PATENT STATUS IN LMICS
DDi (Rif)	Treatment	PrEP	Heavily Experienced	Women	Paediatric	Availability/ Affordability	Market size	Expiry and geographical scope
●	● A	● A		★★	★	?	●	●
●	? 2	? 3	★★			?	●	●
?	? 2	NA				?	?	●
●	● A	NA	★	★	★★	●	●	●
●	● A	NA		★	★	?	●	●

- ● High (or better than SOC)
- ● Potential for improvement over SOC
- ● Medium (or comparable to SOC)
- ● Low (or worse than SOC)

- A Approved
- 1 Phase 1
- 2 Phase 2
- 3 Phase 3

- NA Not applicable
- ? Too early to assess
- * New entry

★ At least one study is ongoing for the specific population

★★ At least one study is ongoing and drug features are particularly promising for the specific population

None Drug not assessed for the specific population

3.2 DETAILED MPP ASSESSMENT IN HIV

Table 3 below provides additional information on the HIV medicines that are being prioritised for in-licensing by MPP, with some details on each medicine along the various criteria being used for prioritisation, while table 4 outlines the watchlist for HIV.

TABLE 3. MPP PRIORITIES IN HIV

PRODUCT *Originator(s)*	**MPP ASSESSMENT**
Cabotegravir for PrEP *(ViiV Healthcare)*	**Clinical Relevance** Cabotegravir is an approved drug for the treatment of HIV in virally suppressed adults in combination with rilpivirine, and alone as injectable for HIV PrEP. It was developed by ViiV Healthcare and has received regulatory approval for treatment in Canada, Europe, US and Australia. More recently, Cabotegravir standalone intramuscularly injectable formulation (CAB-LA) has been approved for PrEP by the US FDA[8]. **Cabotegravir Entity** Cabotegravir is a small molecule belonging to the HIV-1 integrase strand transfer inhibitor (INSTI)[9]. Despite a higher genetic barrier compared to first generation INSTIs (such as elvitegravir and raltegravir), the development of specific mutations (like Q148R/K) may be a concern for high-level cross-resistance to all INSTIs[10]. **Cabotegravir for HIV treatment** Cabotegravir is approved as 1-2 month intramuscular injectable (400mg and 600mg) co-packed with rilpivirine and commercialised as Cabenuva[11,12]. However, the cold chain requirement of rilpivirine might render this combination less suitable for use in some resource-limited settings. Before starting on the long-acting injectable formulation, daily oral cabotegravir (30 mg tablets) is also available to be used as lead-in for the long-acting formulation as prescribed. Alternatively, other formulations and administration routes are being investigated, like microarray patches and subdermal implants. **Cabotegravir for HIV PrEP** Recently, injectable long-acting cabotegravir (CAB-LA), commercialised as Apretude, has been approved by the US FDA for PrEP for adults and adolescents at risk of sexually acquiring HIV. This long-acting formulation for PrEP could increase adherence and ease pill burden and represents an alternative prevention option for people at risk of acquiring HIV-1. Apretude is given first as two initiation injections administered one month apart, and then every two months thereafter. The FDA approval decision was based on results showing that long-acting cabotegravir is more effective than daily oral TDF/FTC at preventing HIV-1 infection[13,14]. **Safety** Cabotegravir is generally safe and well tolerated. Most frequently reported adverse reactions from monthly and bi-monthly dosing studies were injection site reactions (up to 84%), headache (up to 12%) and pyrexia (10%)[12,13,15]. The pharmacokinetic tail of cabotegravir injections, however, raises some concerns about the potential emergence of drug resistance in the event of interruption of PrEP based on CAB-LA in the absence of medical follow-up[16]. In the context of HIV treatment, excessive weight-gain is an emerging safety concern among PLHIV on ART[17,18]. Despite the modest weight gain effect shown in the FLAIR, ATLAS and ATLAS-2M studies, the contribution of confounding factors, like the "return-to-health-effect", is still unclear and makes it challenging to conclude on the effect of cabotegravir on weight gain during HIV treatment regimens. It will be important to continue monitoring data to understand the effects on weight and the risk factors associated with it. Cabotegravir co-administration with other therapies may result in loss of virologic response because of drug-drug interactions and specifically: anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin), glucocorticoids (dexamethasone)[19], and potentially, drugs altering the activity of UGT1A1 and UGT1A9 enzymes[20]. Interactions with antimycobacterials (rifabutin, rifampin, rifapentine) may represent a challenge.

8 https://www.fda.gov/news-events/press-announcements/fda-approves-first-injectable-treatment-hiv-pre-exposure-prevention

9 https://pubs.acs.org/doi/pdf/10.1021/acs.oprd.9b00031?src=recsys

10 https://retrovirology.biomedcentral.com/articles/10.1186/s12977-018-0440-3

11 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.

12 https://pubmed.ncbi.nlm.nih.gov/35760225/

13 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)00538-4/fulltext

14 https://www.nejm.org/doi/full/10.1056/NEJMoa2101016

15 Landovitz. CROI 2022. Abstr 96

16 https://www.nature.com/articles/s41467-019-10047-w

17 https://www.ema.europa.eu/en/documents/product-information/vocabria-epar-product-information_en.pdf

18 https://pubmed.ncbi.nlm.nih.gov/35706487/

19 https://www.ema.europa.eu/en/documents/product-information/vocabria-epar-product-information_en.pdf

20 https://link.springer.com/article/10.1007/s40262-021-01005-1

PRODUCT *Originator(s)*	MPP ASSESSMENT
Cabotegravir for PrEP *(ViiV Healthcare)*	Additionally, cabotegravir did not significantly change ethinyl estradiol, levonorgestrel and medroxyprogesterone acetate plasma concentrations to a clinically relevant extent, making it compatible with most used contraceptive options in LMICs[21,22]. Finally, cabotegravir is also being studied during pregnancy, in lactating individuals, and in children older than 12 years[23,24], but no results have been released so far. **Access** Detailed access plans in LMICs are currently under development, it is therefore not possible to assess what will be the availability and affordability of the product in these countries at this stage. There are concerns about the logistical and health systems challenges linked to service delivery and the impact this could have on scale-up. Nevertheless, the market for oral PrEP has been increasing significantly over the past two years, with over half of PrEP initiations taking place in LMICs. In addition, some studies have suggested that injectable formulations could be preferred by certain at-risk populations, which suggests that CAB-LA may be a very valuable option for HIV prevention among some groups, in particular, but not limited to, adolescents and women, including in LMICs[25]. While there are some known complexities in the development and regulatory pathway for generic injectable cabotegravir, possibly requiring third-party investment to reduce development costs, there appears to be significant interest from generic manufacturers and licensing of generic CAB-LA could contribute to broader access to the product in LMICs and improved affordability. In May 2022, ViiV announced its commitment to grant a voluntary licence for patents relating to CAB-LA for PrEP to the MPP[26]. **Patent Status in LMICs** Patents on the cabotegravir compound (which are the same as for the dolutegravir compound) are filed or granted in several LMICs and expected to expire in 2026. Patents on the long-acting parenteral composition are also filed or granted in several LMICs and expected to expire in 2031.
Lenacapavir *(Gilead Sciences)*	**Clinical Relevance** Lenacapavir is Gilead's investigational phase II/III ARV being studied for HIV treatment. **Lenacapavir Entity** Lenacapavir is a small molecule belonging to the capsid inhibitors class[27], a new class of drugs that function by interfering with the assembly and disassembly of the viral capsid by targeting NUP153 and CSF6 proteins. Because lenacapavir is a first-in-class ARV, it does not show cross-resistance with other ARV classes[28]. Lenacapavir-resistant HIV mutants showed decreased replication capacity, suggesting reduced viral fitness[29]. Its high potency and long half-life make it a suitable candidate for long-acting formulations[30] that can increase adherence and ease pill burden in PLHIV. **Lenacapavir for HIV treatment in naïve patients** Lenacapavir is being studied in combination with other ARVs (LEN+ F/TAF, LEN+TAF or LEN+F/TAF+BIC) for the treatment of HIV naïve patients (CALIBRATE study, in phase II)[31]. Recently, it has been shown that 93% of treated patients that were virologically suppressed at week 28, also maintained virologic suppression at week 54. Attention should be paid to the emergence of capsid mutations conferring high level LEN resistance, even if the clinical implications are not yet clear and more data is needed[32]. **Lenacapavir for HIV treatment in Heavily Treatment-Experienced HIV patients** Sub-cutaneous injection of lenacapavir is being studied in heavily treatment-experienced HIV patients with multidrug resistance (CAPELLA study in Phase II/III)[33]. At week 52, 83% patients were virologically suppressed, suggesting that lenacapavir injection every 6 months is effective at maintaining virological suppression[34]. Based on the CAPELLA study data, lenacapavir received positive opinion from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA), a key step toward market approval[35,36].

21 https://clinicaltrials.gov/ct2/show/NCT02159131
22 https://www.researchgate.net/publication/354135324_Sexually_transmitted_infections_and_depot_medroxyprogesterone_acetate_do_not_impact_protection_from_SHIV_acquisition_by_long-acting_cabotegravir_in_macaques
23 https://clinicaltrials.gov/ct2/show/NCT04518228
24 https://clinicaltrials.gov/ct2/show/NCT03497676
25 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6717317/
26 https://viivhealthcare.com/hiv-news-and-media/news/press-releases/2022/may/viiv-healthcare-commits-to-grant-voluntary-licence-for-patents
27 https://pubmed.ncbi.nlm.nih.gov/32612233/
28 https://i-base.info/htb/39080
29 CROI2021- ACTIVITY AND RESISTANCE CHARACTERIZATION OF THE HIV CAPSID INHIBITOR LENACAPAVI
30 https://programme.aids2020.org/Abstract/Abstract/8533
31 https://clinicaltrials.gov/ct2/show/NCT04143594
32 Gupta. CROI 2022. Abstr 138.
33 https://clinicaltrials.gov/ct2/show/NCT04150068
34 Ogbuagu. CROI 2022. Abstr 491
35 https://www.nejm.org/doi/full/10.1056/NEJMoa2115542?query=featured_home
36 https://www.gilead.com/news-and-press/press-room/press-releases/2022/6/investigational-lenacapavir-receives-positive-chmp-opinion-for-people-with-multi-drug-resistant-hiv

PRODUCT *Originator(s)*	MPP ASSESSMENT
Lenacapavir *(Gilead Sciences)*	**Lenacapavir for HIV PrEP** 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[37]. **Safety** Lenacapavir is generally well tolerated and with a promising safety profile with most common adverse events being headache, nausea, cough and diarrhoea and no sign of renal toxicity[38]. However, important drug-drug interactions could limit co-administration[39]. It is currently advised not to co-administer lenacapavir with potent CYP/P-gp/UGT inducers (like rifampicin). Studies are in progress to understand the possibility of co-administration with moderate CYP/P-gp/UGT inducers (like efavirenz). Given that lenacapavir has a mechanism of action different from current ARVs, it will be important to understand the effects of capsid inhibitors on potential weight-gain and associated metabolic risks. **Access** Access plans for LMICs are not yet known. While the company has had a licensing policy for its other ARVs, details on its access strategy for lenacapavir are not yet known. **Patent Status in LMICs** Several patents on lenacapavir have been filed or granted in LMICs expiring between 2034 and 2037[40].

Table 4 below provides details on the HIV medicines that are being included in the MPP watchlist, with some details on each medicine along the various criteria being used for prioritisation.

TABLE 4. MPP WATCHLIST IN HIV

PRODUCT *Originator(s)*	MPP ASSESSMENT
Doravirine *(Merck Sharp and Dohme)*	**Clinical Relevance** Doravirine is an FDA and EMA approved drug developed by Merck Sharp and Dohme for the treatment of HIV and is also being studied for PrEP and PEP. It should be noted that clinical trials of doravirine in combination with islatravir have been placed on-hold by FDA because of safety concerns on islatravir. **Doravirine Entity** Doravirine is a small molecule belonging to the class of non-nucleoside reverse transcriptase inhibitor (NNRTI) that inhibits HIV replication by non-competitive inhibition of HIV reverse transcriptase[41]. Doravirine is available as 100 mg oral tablets and in a fixed dose combination with tenofovir and lamivudine. **Doravirine for HIV treatment in naïve patients** Doravirine is approved, in combination with lamivudine and tenofovir disoproxil fumarate, for the treatment of HIV-1 infection in adult patients with no prior antiretroviral treatment history. The regulatory approval was based on the results of the DRIVE studies. DRIVE-FORWARD was a phase III study comparing doravirine to darunavir boosted with ritonavir with investigator selected NRTI backbone therapy. DRIVE-AHEAD was a phase III study comparing doravirine/lamivudine/tenofovir disoproxil fumarate to efavirenz/emtricitabine/tenofovir disoproxil fumarate. Both DRIVE studies were designed as non-inferiority trials and demonstrated doravirine to be non-inferior to the comparators used. **Doravirine for HIV treatment in Heavily Treatment-Experienced HIV patients** Doravirine is also being studied in combination with islatravir in heavily treatment-experienced HIV patients having at least triple-class resistance[42] and it is also proposed as an alternative in adults living with HIV experiencing virological failure on first line efavirenz-based antiretroviral therapy with NNRTI resistance (ADORE study)[43]. **Doravirine for HIV PEP** Doravirine is also being studied for non-occupational post exposure prophylaxis[44].

37 CROI2021 - LENACAPAVIR (GS-6207): FIRST CLINICALLY ACTIVE LONG-ACTING INHIBITOR OF HIV CAPSID
38 CROI2021- POTENT ANTIVIRAL ACTIVITY OF LENACAPAVIR IN PHASE 2/3 IN HEAVILY ART-EXPERIENCED PWH
39 https://pubmed.ncbi.nlm.nih.gov/35746673/
40 https://www.medspal.org/?product%5B%5D=Lenacapavir&page=1
41 https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210806s000lbl.pdf
42 https://clinicaltrials.gov/ct2/show/NCT04233216
43 https://clinicaltrials.gov/ct2/show/NCT04429152
44 https://clinicaltrials.gov/ct2/show/NCT04233372

PRODUCT *Originator(s)*	MPP ASSESSMENT
Doravirine *(Merck Sharp and Dohme)*	**Doravirine for Paediatric HIV** Doravirine is also being studied in combination with islatravir in paediatric participants with HIV who are <18 years of age and weigh ⩾35 kg[45] (now on hold). Doravirine is particularly interesting for its potential as treatment for infants[46]. It is studied in HIV infected children starting from 4 weeks of age up to 12 years and weighting less than 45 kg[47]. Additionally, a granular oral formulation has been developed[48]. **Safety** The DRIVE trials demonstrated that doravirine is efficacious over long periods of time while maintaining an acceptable safety profile. Most common adverse reactions (incidence greater than or equal to 5%, all grades) were nausea, dizziness, headache, fatigue, diarrhoea, abdominal pain, and abnormal dreams. It should be noted that doravirine is contraindicated with rifampicin and rifapentine, which are important WHO-recommended TB medicines. However, a recent study suggests that twice-daily doravirine could overcome the interaction effect from once-weekly rifapentine and isoniazid[49] , based on a study in healthy volunteers[50]. Doravirine is also being studied as a possible alternative for people experiencing excessive weight gain on integrase inhibitors[51], however, no results are available yet. The safety of doravirine is also being studied in women of reproductive potential living with HIV in South Africa[52], as well as its possible drug interactions with estradiol and spironolactone, a component of feminising hormone therapy in healthy transgender women[53]. **Access** Doravirine's availability in LMICs remains very low and is generally not provided in most treatment programs. This is likely because it is not recommended by WHO and because generic versions are not yet available. Licences to a small number of LMICs are known to have been granted, but no details are publicly available and generic versions are not yet on the market. **Patent Status in LMICs** Patents on the doravirine compound have been filed in many LMICs and are expected to expire in 2031[54] .
GSK3640254 *(ViiV Healthcare)*	**Clinical Relevance** GSK3640254 (GSK'254) is a ViiV Healthcare investigational phase IIb ARV being studied for daily oral HIV treatment of naïve patients[55,56]. **GSK3640254 Entity** GSK3640254 is a small molecule belonging to the maturation inhibitors class, which targets the HIV structural protein (Gag) and inhibits viral maturation by protease-mediated cleavage of CA-SP1 in the Gag polyprotein[57]. Because of the new mechanism of action, GSK3640254 could have low cross-resistance with other approved ARV classes. GSK3640254 can be administered orally (dosage to be selected between 140mg and 200 mg)[58] and without food restrictions[59]. **GSK3640254 for HIV treatment of naïve patients** GSK3640254 is currently being studied in a phase II study in combination with ABC/3TC or FTC/TAF[60] using dolutegravir as comparator, suggesting that GSK3640254 could be used as a dolutegravir-based regimen alternative. A promising dose-response effect (10-200mg range) was seen recently in GSK3640254 treated naïve patients. However, some patients developed phenotypic resistance raising concerns about possible pre-existing variants. The study was limited in time and number of patients; therefore, it will be important to follow the future development of GSK3640254 efficacy data. **Safety** GSK3640254 safety data is limited but encouraging[61]. It can be co-administered with DTG[62], TAF/FTC[63] and oral contraceptives (ethinyl estradiol and levonorgestrel)[64] .

45 https://clinicaltrials.gov/ct2/show/NCT04295772
46 https://www.ema.europa.eu/en/documents/pip-decision/p/0115/2017-ema-decision-21-april-2017-acceptance-modification-agreed-paediatric-investigation-plan_en.pdf
47 https://clinicaltrials.gov/ct2/show/NCT04375800
48 https://link.springer.com/article/10.1208/s12249-020-1630-6?shared-article-renderer
49 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7719366/
50 https://clinicaltrials.gov/ct2/show/NCT03886701
51 https://clinicaltrials.gov/ct2/show/NCT04636437
52 https://clinicaltrials.gov/ct2/show/NCT04097925
53 https://clinicaltrials.gov/ct2/show/NCT04283656
54 https://www.medspal.org/?product%5B%5D=Doravirine+100+mg&product%5B%5D=Doravirine%2FLamivudine%2FTenofovir+100%2F300%2F300+mg&-page=1
55 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8765437/
56 https://pubmed.ncbi.nlm.nih.gov/34996113/
57 https://seekingalpha.com/article/4165622-new-generation-of-novel-hiv-small-molecule-antivirals
58 https://clinicaltrials.gov/ct2/show/study/NCT03575962
59 https://clinicaltrials.gov/ct2/show/record/NCT04263142
60 https://clinicaltrials.gov/ct2/show/record/NCT04493216
61 https://pubmed.ncbi.nlm.nih.gov/33200887/
62 https://pubmed.ncbi.nlm.nih.gov/33533507
63 https://www.natap.org/2020/Pharm/Pharm_12.htm
64 https://www.natap.org/2020/Pharm/Pharm_08.htm

PRODUCT *Originator(s)*	MPP ASSESSMENT
GSK3640254 *(ViiV Healthcare)*	Current drug-drug interaction studies are evaluating the possible co-administration of GSK3640254 with darunavir/ritonavir[65], caffeine, metoprolol, montelukast, flurbiprofen, omeprazole, midazolam, digoxin, and pravastatin[66] and moxifloxacin[67]. Given that GSK3640254 has a mechanism of action different from current ARVs, it will be important to understand the effects of maturation inhibitors on potential weight-gain and associated metabolic risks. The final product safety profile will be influenced by drug combinations and formulation. GSK3640254 can be administered orally (dosage to be selected between 140mg and 200 mg)[68] and without food restrictions[69]. **Access** Access plans for LMICs are not yet known. **Patent Status in LMICs** Compound patents on GSK3640254 have been filed or granted in many LMICs, expiring in 2035[70].
Rilpivirine *(Janssen)*	**Clinical Relevance** Rilpivirine is an approved drug developed by Tibotec/Janssen for the treatment of HIV-1, in combination with other antiretroviral agents in treatment-naïve adult patients infected with HIV-1[71]. **Rilpivirine Entity** Rilpivirine is a small molecule belonging to the NNRTI class[72]. The observed virologic failure rate in rilpivirine treated subjects suggests a higher rate of overall treatment resistance and cross-resistance to the other NNRTI drugs compared to efavirenz[73]. Additionally, higher virologic failure has been noticed also in subjects starting rilpivirine treatment with HIV-1 RNA greater than 100,000 copies/mL and subjects having CD4+ cell count less than 200 cells/mm^3 ([74]). Rilpivirine is approved as a monthly intra-muscular injectable (900mg or 600mg) co-packed with cabotegravir[75]. This long-acting formulation could increase adherence and ease pill burden in PLHIV. However, the cold chain requirement of rilpivirine injections makes it less suitable for use in resource-limited settings. Rilpivirine also exists as a daily 25 mg tablet as lead-in before starting long-acting injectable formulation or as treatment in combination with other ARVs. However, rilpivirine exposure in oral formulations is approximately 40% lower when in a fasted condition compared to following a normal caloric meal, making it less convenient. **Rilpivirine for HIV treatment in virologically suppressed patients and naïve patients** Rilpivirine is approved as long-acting intramuscular injectable in combination with cabotegravir for the treatment of virally suppressed HIV patients (Cabenuva). Recently, Viiv announced the label update for Cabenuva, which can be initiated with or without an oral lead-in period[76]. FLAIR and ATLAS studies showed rilpivirine to be non-inferior to current antiretroviral regimen arm. The study ATLAS-2M showed that virologic suppression rates remained high with 86.9% and 88.2% in the monthly and 2-months dosing arms, suggesting that LA CAB + RPV injections given Q8W remained effective through 152 weeks when compared with Q4W administration[77]. Rilpivirine is approved, in combination with other antiretroviral agents (including FTC/TDF), for treatment-naïve adult patients infected with HIV-1. **Rilpivirine for HIV PrEP** The safety and acceptability of long-acting rilpivirine is being studied as PrEP as a 1200 mg IM injection at eight-week intervals[78] . This study found that long-acting injectable PrEP is acceptable among African and US women.

65 https://clinicaltrials.gov/ct2/results?term=GSK3640254&cond=HIV&Search=Apply&recrs=b&recrs=a&recrs=f&recrs=d&recrs=g&recrs=h&recrs=i&recrs=m&age_v=&gndr=&type=&rsl=

66 https://clinicaltrials.gov/ct2/show/NCT04563845

67 https://clinicaltrials.gov/ct2/show/NCT04563845

68 https://clinicaltrials.gov/ct2/show/study/NCT03575962

69 https://clinicaltrials.gov/ct2/show/record/NCT04263142

70 https://www.medspal.org/?product%5B%5D=GSK3640254&page=1

71 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202022Orig1s000TOC.cfm

72 https://pubmed.ncbi.nlm.nih.gov/22519768/

73 https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202022s000lbl.pdf

74 https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/202022s008lbledt.pdf

75 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.

76 https://www.gsk.com/en-gb/media/press-releases/viiv-healthcare-announces-label-update-for-its-long-acting-hiv-treatment-cabenuva-cabotegravir-rilpivirine-to-be-initiated-with-or-without-an-oral-lead-in-period/

77 Overton. CROI 2022. Abstr 479.

78 https://clinicaltrials.gov/ct2/show/NCT02165202

PRODUCT *Originator(s)*	MPP ASSESSMENT
Rilpivirine *(Janssen)*	**Rilpivirine for HIV PEP** Rilpivirine, co-formulated with tenofovir-emtricitabine, is being evaluated in a phase IV study as HIV nonoccupational post-exposure prophylaxis in men who have sex with men[79] . **Rilpivirine for Paediatric HIV** Rilpivirine is also being studied in HIV-infected children and adolescents as oral and long-acting injectable with cabotegravir (phase I/II MOCHA study)[80]. **Safety** Caution should be given when rilpivirine is prescribed in patients using drugs with a known risk of Torsade de Pointes (a type of polymorphic ventricular tachycardia). Severe skin and hypersensitivity reactions have been reported during post-marketing surveillance with rilpivirine-containing regimens. Additionally, severe depressive disorders and hepatotoxicity have been reported. The most common adverse drug reactions (incidence > 2%) of at least moderate to severe intensity (> Grade 2) were depression, insomnia, headache and rash[81]. Rilpivirine cannot be used in combination with other NNRTIs, and its plasma concentrations may change with co-administration with drugs that induce or inhibit CYP3A4, including rifampicin[82]. **Access** Licences on oral formulations of rilpivirine were granted to several companies in 2012, covering 112 countries, but generic versions have not yet entered the market. Access plans for the long-acting formulation of rilpivirine are not known. **Patent Status in LMICs** While patents on rilpivirine compound are expiring in 2021 and 2022, there are patents on the aqueous suspensions of rilpivirine micro- or nanoparticles (relevant to the long-acting formulation) that have been granted in several LMICs and expire in 2027. There are also patents pending or granted on combinations of rilpivirine that are relevant to combinations with tenofovir disoproxil fumarate and tenofovir alafenamide. The long-acting formulation of rilpivirine remains in the watchlist, as it could represent an interesting tool for treatment in LMICs, together with cabotegravir, if it were reformulated as a heat-stable formulation.

79 https://clinicaltrials.gov/ct2/show/NCT01715636
80 https://clinicaltrials.gov/ct2/show/NCT03497676
81 https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202022s000lbl.pdf
82 https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202022s000lbl.pdf

4. MPP PRIORITISATION IN TUBERCULOSIS

4.1 GRAPHICAL SUMMARY OF MPP PRIORITIES FOR TUBERCULOSIS

The table below provides a graphical summary of MPP priorities and watchlist in the field of tuberculosis (TB). One TB medicine remains a priority for in-licensing for the fourth year in a row. Six other medicines are in MPP watchlist as it is considered that there is currently insufficient clinical data at this stage to prioritise them for licensing.

TABLE 5. SUMMARY TABLE IN TB

					EASE OF ADMINISTRATION		SAF
	SRA approval	WHO recommended	Number of years in MPP Priority List	New MoA	Oral formulation	Long-acting formulation	Side effects
MPP Priorities							
Bedaquiline	Yes	Yes	4	Yes	●	NA	○
MPP Watchlist							
BTZ-043	No	No	NA	Yes	○	NA	?
Delpazolid	No	No	NA	No	○	NA	?
GSK 3036656	No	No	NA	Yes	○	NA	?
Macozinone	No	No	NA	Yes	○	NA	?
OPC-167832	No	No	NA	Yes	○	NA	?
Telacebec	No	No	NA	Yes	○	NA	?

PILLAR 1					PILLAR 2		PILLAR 3
ETY	EFFICACY		SPECIAL POPULATIONS		ACCESS CHALLENGES		PATENT STATUS IN LMICS
DDi	DS-TB	DR-TB	Women	Paediatric	Availability/ Affordability	Market size	Expiry and geographical scope
●	? 2	● A	★	● A	●	●	●
?	? 2	NA			?		●
?	? 2	NA			?		●
?	? 2	NA			?		●
?	? 2	NA			?		●
?	? 2	NA			?		●
?	? 2	NA			?		●

● High (or better than SOC)
● Medium (or comparable to SOC)
● Low (or worse than SOC)
NA Not applicable
? Too early to assess

A Approved
1 Phase 1
2 Phase 2
3 Phase 3

★ At least one study is ongoing for the specific population
None Drug not assessed for the specific population

4.2 DETAILED MPP ASSESSMENTS IN TUBERCULOSIS

Table 6 below provides additional information on the TB medicine that has been prioritised for in-licensing by MPP, with some details along the various criteria being used for prioritisation.

TABLE 6. MPP PRIORITY FOR TB

PRODUCT *Originator(s)*	**MPP ASSESSMENT**
Bedaquiline *(Janssen)*	**Clinical Relevance** Bedaquiline is an US FDA and EMA approved drug developed by Janssen for the treatment of multidrug resistant TB. Bedaquiline is a diarylquinoline targeting the adenosine triphosphate (ATP) synthase enzyme, which is essential for energy supply of the Mycobacterium tuberculosis. Bedaquiline is also studied for drug-sensitive TB[83]. As per WHO guidelines[84], bedaquiline has been recommended as part of various regimens for MDR-TB. Given WHO's recommendation, a full clinical assessment of bedaquiline is not undertaken and MPP considers the drug as a clinical priority in view of that recommendation. **Access** A discounted price of USD 340 for the six-month course of bedaquiline was announced with the Global Drug Facility in July 2020, with the possibility of further discounts based on volumes[85]. In view of such discounts, the price in 2020 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 countries with no secondary patents on BDQ, it is expected that generic manufacturers are likely to enter the market at that time, which will likely lead to price reductions in such countries. For other countries with secondary patents, generic market entry may need to wait until 2027. A licence could contribute to accelerate access to the generics in such countries.

Table 7 below provides details on the TB medicines that are being included in the MPP Watchlist, with some details on each medicine along the various criteria being used for prioritisation.

TABLE 7. MPP WATCHLIST IN TB

PRODUCT *Originator(s)*	**MPP ASSESSMENT**
BTZ-043 *(University of Munich and the German Center for Infection Research)*	**Clinical Relevance** BTZ-043 is an investigational phase II drug developed by the University of Munich and the German Center for Infection Research (DZIF) and is being studied for TB treatment. BTZ-043 is a benzothiazinone which efficiently inhibits Mycobacterium tuberculosis cell wall synthesis by blocking the decaprenyl- phosphoribose-2'-epimerase (DprE1), necessary for bacterial replication. Its mechanism of action is highly selective for mycobacterial species. Results from a phase Ia single ascending dose study proved BTZ-043 to be safe and well tolerated up to 500 mg[86]. A new phase Ib/IIa multiple ascending dose study to evaluate the safety, tolerability, PK, drug-drug interaction and bactericidal activity of BTZ-043 (daily oral dose) administered over 14 days to 77 drug sensitive-TB participants was initiated in November 2019[87], but the results have not been published yet. **Access** Access plans for BTZ-043 in LMICs are unknown. **Patent Status in LMICs** The compound patent on BTZ-043 has been filed or granted in some LMICs and is expected to expire in 2026. Secondary patents have not been identified.

83 https://clinicaltrials.gov/ct2/show/NCT03338621
84 https://www.who.int/tb/publications/2019/rapid_communications_MDR/en/
85 http://www.stoptb.org/news/stories/2020/ns20_024.html
86 https://clinicaltrials.gov/ct2/show/NCT0359060
87 https://clinicaltrials.gov/ct2/show/NCT04044001

PRODUCT *Originator(s)*	MPP ASSESSMENT
Delpazolid (LCB-01371) *(LegoChem BioSciences)*	**Clinical Relevance** Delpazolid is an investigational phase II drug developed by LegoChem BioSciences Inc.[88] and is studied for TB treatment. Delpazolid is an oxazolidinone which inhibits protein synthesis in *Mycobacterium tuberculosis*. A phase II trial to evaluate early bactericidal activity, safety and pharmacokinetics was completed in February 2020[89], which showed a decline in TB bacterial count in patients treated with delpazolid, however more data is needed to understand how this result may translate into clinical practice[90]. A phase IIb dose-finding study has been planned for delpazolid, in combination with bedaquiline, delamanid and moxifloxacin, to treat adult patients with newly diagnosed, smear positive, uncomplicated, drug sensitive pulmonary tuberculosis (TB)[91]. **Access** Access plans for delpazolid in LMICs are unknown. **Patent Status in LMICs** The compound patent on delpazolid has been filed or granted in some LMICs and is expected to expire in 2029.
GSK3036656 *(GlaxoSmithKline)*	**Clinical Relevance** GSK3036656 is an investigational phase II drug developed by GlaxoSmithKline for the treatment of tuberculosis. GSK3036656 is an oxaborole which inhibits the leucyl-tRNA synthetase blocking protein synthesis in *Mycobacterium tuberculosis*. It was found to be well tolerated in healthy adults as per the phase I single & multiple dose ascending studies[92]. A phase IIa study is now in progress to investigate the early bactericidal activity, safety and tolerability of GSK3036656 in sequential cohorts of subjects with rifampicin-susceptible tuberculosis[93]. **Access** Access plans for GSK3036656 in LMICs are unknown. **Patent Status in LMICs** Patents on GSK3036656 have been filed or granted in several LMICs and are expected to expire in 2031-2036.
Macozinone (PBTZ-169) *(Swiss Federal Institute of Technology Lausanne (EPFL))*	**Clinical Relevance** Macozinone is an investigational phase II drug developed by the non-profit Innovative Medicines for Tuberculosis (iM4TB) foundation[94]. Macozinone is a benzothiazinone that covalently inhibits DprE1, the enzyme essential for the biosynthesis of key cell wall components and necessary for *Mycobacterium tuberculosis* replication. It is a derivative, optimized by medicinal chemistry from the lead BTZ-043, having easier chemical synthesis, low cost of goods and better pharmacodynamics. The company Nearmedic Plus leads macozinone development for the Russian market and associated countries. The company completed an open label, dose-escalation phase I study in healthy male volunteers followed by a multiple ascending dose, showing promising safety profile of the drug[95]. More recently, a Nearmedic Plus phase IIa study was terminated due to slow enrolment[96]. This study aimed to evaluate the early bactericidal activity of macozinone 80 mg capsules in drug-sensitive TB patients in Russia and Belarus. **Access** Access plans for macozinone in LMICs are unknown. **Patent Status in LMICs** The compound patent on macozinone has been filed or granted in some LMICs and is expected to expire in 2031.

88 https://www.legochembio.com/pipeline/pipeline.php?lang=e&cate=12#catepoint
89 https://clinicaltrials.gov/ct2/show/NCT02836483
90 https://pubmed.ncbi.nlm.nih.gov/34871098/
91 https://clinicaltrials.gov/ct2/show/NCT04550832
92 https://clinicaltrials.gov/ct2/show/NCT03075410
93 https://clinicaltrials.gov/ct2/show/NCT03557281
94 https://im4tb.org/
95 https://clinicaltrials.gov/ct2/show/NCT03036163
96 https://clinicaltrials.gov/ct2/show/NCT03334734

PRODUCT *Originator(s)*	MPP ASSESSMENT
OPC-167832 *(Otsuka)*	**Clinical Relevance** OPC-167832 is an Otsuka investigational phase II drug being studied for TB treatment[97] . OPC-167832 is a carbostyril derivative which showed anti-mycobacterial activity by inhibiting decaprenylphosphoryl-β-D-ribose 2'-oxidase (DprE1), an essential enzyme for cell wall biosynthesis of Mycobacterium tuberculosis. It showed potent bactericidal activity (0.00024 to 0.002 μg/mL) against both growing and intracellular bacilli. This compound is being developed in a phase I/II trial of multiple oral doses of OPC-167832 for uncomplicated pulmonary tuberculosis by Otsuka, in collaboration with the Bill and Melinda Gates Foundation[98]. A recent publication from Otsuka has suggested that OPC-167832 in regimens combined with delamanid showed superior efficacy to a standard regimen RHZE (rifampicin, isoniazid, pyrazinamide and ethambutol) in mice[99]. **Access** Access plans for OPC-167832 in LMICs are unknown. **Patent Status in LMICs** The compound patent on OPC-167832 has been filed or granted in several LMICs and is expected to expire in 2035.
Telacebec (Q203) *(Qurient Co. Ltd)*	**Clinical Relevance** Telacebeq is a Qurient investigational phase II drug studied for TB treatment[100]. Telacebec is a first-in-class selective inhibitor of the *Mycobacterium tuberculosis* cytochrome bc1 complex, which is a critical component of the bacteria energy metabolism[101]. A phase IIa trial showed promising early bactericidal activity in March 2020[102]. The study showed that daily treatment with oral telacebec (100 to 300 mg) reduced the number of live TB bacteria in a dose dependent manner. TB load was assessed in sputum samples collected from 61 patients diagnosed with rifampicin- and isoniazid-susceptible pulmonary tuberculosis. No serious adverse events were reported in this phase IIa study as well as in the previous studies[103,104], suggesting a promising safety profile. **Access** Access plans for telacebec in LMICs are unknown. **Patent Status in LMICs** The compound patent on telacebec has been filed or granted in several LMICs and is expected to expire in 2031.

In addition to the medicines discussed above, MPP also assessed two other tuberculosis medicines, both of which are currently recommended in WHO guidelines: delamanid and pretomanid. The decision not to prioritise them was based on the current access and IP situation of those two medicines. With respect to delamanid, the existence of an exclusive license on delamanid to one generic manufacturer means that there would not be a role for MPP in relation to that medicine. With respect to pretomanid, the product was developed by a public health organisation 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.

97 https://www.otsuka-us.com/research
98 https://clinicaltrials.gov/ct2/show/NCT03678688
99 https://aac.asm.org/content/aac/early/2020/03/25/AAC.02020-19.full.pdf
100 http://www.qurient.com/bbs/content.php?co_id=q203#download_0
101 https://pubmed.ncbi.nlm.nih.gov/32212527/
102 https://clinicaltrials.gov/ct2/show/NCT03563599
103 https://clinicaltrials.gov/ct2/show/NCT02530710
104 https://clinicaltrials.gov/ct2/show/NCT02858973

5. LONG-ACTING FORMULATIONS AND TECHNOLOGIES

In 2019, MPP initiated an exploratory phase for potentially expanding its mandate to work on long-acting medicines that could contribute to improving adherence to treatments and treatment outcomes. The exploratory phase concluded that MPP could play an important role in facilitating the development of, and access to, new long-acting (LA) formulations that could be important in LMICs. As part of this engagement, MPP has developed LAPaL, a free online crowdsourced repository for long-acting technologies and their applications with potential impact for global health, with the aim of facilitating collaborations in the long-acting space and advocate for access to LA therapeutics[105].

In addition to the formulation prioritised here, MPP has acquired licenses for two long-acting technologies: a long-acting injectable for HIV treatment based on DcNP technology (University of Washington) and long-acting formulations for malaria and tuberculosis prevention, and for hepatitis C cure, based on Emulsion-Templated Freeze Drying (ETFD) technology (Consortium led by the University of Liverpool). These candidate formulations are in pre-clinical stages.

MPP priority for in-licensing in the long-acting space is listed in table 8.

TABLE 8. PRIORITY LONG-ACTING FORMULATION FOR IN-LICENSING

PRODUCT *Originator(s)*	**MPP ASSESSMENT**
Long-acting ivermectin depot based on MedinCell's BEPO® technology[106] for malaria vector control *(MedinCell)*	Based on its BEPO® technology, MedinCell is developing a long-acting ivermectin injectable formulation for malaria vector control[107,108]. The formulation uses the BEPO technology to form a fully bioresorbable depot once injected subcutaneously. The product is currently in pre-clinical development, with phase 1 trial planned to start in 2023. It would be administered at the community level in malaria endemic areas, 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[109]. 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[110,111,112,113,114].

105 https://lapal.ch/

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

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

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

109 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

110 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

111 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

112 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

113 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

114 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

6. NON-COMMUNICABLE DISEASES AND CONDITIONS

In 2018, MPP conducted a feasibility study, exploring the expansion of our mandate to include other patented priority essential medicines beyond HIV, hepatitis C and tuberculosis. The study highlighted the expected public health value of providing generic access to patented products on the WHO Essential Medicines List (EML). The organisation's remit now covers patented essential medicines included in the WHO EML and those with strong potential for future inclusion.

The aim of this section is to provide an assessment of the priority medicines for in-licensing by MPP that could have an important role in treating non-communicable diseases of public health importance, such as cancer, diabetes and reproductive, maternal, newborn child health (RMNCH) in LMICs. It comprises medicines that are currently included in the WHO Model List of Essential Medicines (EML) or that have strong potential for future inclusion. The updated WHO EML 2021 published on 1st October 2021 included the addition of 20 new medicines to the EML, and 13 to the Essential Medicines List for Children (EMLc). The EML is intended as a guide for countries or regional authorities to adopt or adapt in accordance with local priorities and treatment guidelines for the development and updating of national essential medicines lists. As part of its assessment, the EML Expert Committee considered the comparative cost-effectiveness of submitted medicines and noted the high costs of several drugs that at current prices were not cost-effective compared to standard of care despite having significant clinical benefits. In this vein, the Expert Committee specifically called on MPP to explore licensing possibilities for these 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).

Patented drugs currently in the EML, or those submitted for inclusion, were evaluated through the prioritisation framework described in Table 1 above. While MPP's model to date has focused on small molecules, the organization's mandate has been expanded to include biotherapeutics. As such, MPP is adapting the prioritisation framework for the specific considerations of biotherapeutics. This report includes biotherapeutics recommended by the WHO EML for MPP to explore.

Further, the assessment below includes drugs on the watchlist, as defined in Section 1 above. As most drugs included in the watchlist are in early stages of development, information on current access programmes is limited. As such the assessment focuses on clinical and public health significance. Information on watchlist medicines will be updated as information is made available.

6.1 CANCERS

TABLE 9. MPP PRIORITIES IN CANCERS

PRODUCT *Originator(s)*	**MPP ASSESSMENT**
3rd generation Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Receptor Inhibitor (TKI)	
Osimertinib *(AstraZeneca)*	**Potential EML indication** Osimertinib was submitted for inclusion in the EML for the first line treatment of EGFR+ locally advanced or metastatic non-small cell lung cancer.[115] The WHO EML Expert Committee acknowledged that osimertinib had meaningful overall survival benefit compared to the first- and second-generation tyrosine kinase inhibitors (TKI) currently listed on the EML (erlotinib, gefitinib and afatinib); however, it noted that data is currently immature and that at its current prices, osimertinib has not been found to be cost-effective compared to the first and second generation EGF-TKI's currently on the EML. Further, the Committee called on MPP to explore licensing opportunities for osimertinib and welcomed resubmission in future EML updates. **Clinical Relevance** Over 80% of the 2.2 million incident cases of lung cancer each year are classified as non-small cell (NSCLC). Of these, 30% have the EGFR mutation. Nearly 70% are diagnosed at late stages as locally advanced or metastatic.[116]

115 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

116 https://apps.who.int/iris/handle/10665/330668

PRODUCT *Originator(s)*	MPP ASSESSMENT
Osimertinib *(AstraZeneca)*	The European Society of Medical Oncology considers EFGR TKIs the standard of care for first line treatment for advanced EGFR-mutated NSCLC. EGFR-TKIs have shown an improvement in terms of objective response rate (ORR) and progression free survival (PFS) versus platinum-based chemotherapy[117]. Osimertinib proved to be effective in improving both progression-free and overall survival compared to first and second generation TKIs with a comparable safety profile. (ESMO-MCBS Score= 4).[118,119] **Access** Osimertinib is generally not available or affordable in many LMICs. 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.
Cyclin-dependent kinase (CDK) 4/6 inhibitors	
Ribociclib *(Novartis)* Abemaciclib *(Eli Lilly)* Palbociclib *(Pfizer)*	**Potential EML indication** CDK 4/6 inhibitors were submitted for inclusion in the EML for the treatment of: HR+/HER2- advanced breast cancer.[120] The Expert Committee acknowledged that CD4/6 inhibitors had potential for future inclusion in the EML. However, at the time of submission, survival data were immature, particularly in the first line setting, and at the current high prices the drugs were not found to be cost-effective. The committee recommended that MPP explore the application of its licensing model to these medicines. **Clinical Relevance** ESMO guidelines 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). Studies have found significant advantage of CDK 4/6 inhibitors over endocrine therapy in first-[121,122] or second line[123] setting. The use of CDK4/6 inhibitors showed a significant improvement in survival and quality of life.[124] The safety profile is similar and acceptable for the 3 molecules, with ribociclib having a higher incidence of QT interval prolongation, and abemaciclib having a higher rate of diarrhea and fatigue, but lower rate of hematopoietic SE (including neutropenia).[125,126] **Access** Access programmes are available in a limited number of LMICs. Novartis makes available Emerging Market Brands, which are generally priced at significantly lower price than the global average for the original brand – in India this includes ribociclib.[127] In addition, Novartis and The Max Foundation have recently launched the *"CancerPath to Care"* program that aims to provide access to care to 36,000 people living with breast and rare cancers, like chronic myeloid leukemia (CML), in over 70 LMICs. The breast cancer component, more specifically, will be rolled out in 10 countries by 2023 and expanded to 28 countries by 2025, it foresees donations of both ribociclib and letrozole (an aromatase inhibitor to be used combination).[128] Palbociclib is one of the medicines included in the recently launched initiative *"An Accord for a Healthier World"* through which Pfizer aims to enable sustained, equitable access to high-quality, safe, and effective medicines and vaccines with the potential to improve the health of 1.2 billion people living in 45 lower-income countries around the world.[129] Rwanda, Ghana, Malawi, Senegal, and Uganda are the first 5 countries that have committed to join this initiative, however, further details of what are the key actions to improve access and affordability at country level, are not publicly available yet.

117 https://apps.who.int/iris/handle/10665/330668

118 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

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

120 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

121 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

122 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

123 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

124 https://jnccn.org/configurable/content/journals$002fjnccn$002f17$002f3.5$002farticle-pCLO19-059.xml?t:ac=journals%24002fjnccn%24002f17%24002f3.5%24002farticle-pCLO19-059.xml

125 https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/23rd-expert-committee/a-8-cyclin

126 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6122233/

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

128 https://www.themaxfoundation.org/news/the-max-foundation-announces-cancerpath-to-care-to-treat-up-to-36000-people-living-with-leukemia-breast-and-certain-rare-cancers-in-over-70-low-and-middle-income-countries-by-2025/

129 https://www.pfizer.com/about/responsibility/global-impact/accord

PRODUCT *Originator(s)*	MPP ASSESSMENT
Ribociclib *(Novartis)* Abemaciclib *(Eli Lilly)* Palbociclib *(Pfizer)*	Pfizer has also a patient assistance programme for palbociclib that caps payments to a set number of cycles of product per patient; enables a reduction in the number of paid monthly cycles or payments over a longer period. In Mexico, Pfizer (a) makes the medicine available at public price for patients who attend public hospitals or are referred from hospital patient associations and (b) offers free goods with a purchase of a set number of paid packs to patients based on their socioeconomic status.[130] Access plans for abemaciclib in LMICs are currently unknown. **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.
Bruton's tyrosine kinase inhibitors	
Ibrutinib *(Pharmacyclics INC (AbbVie)/ Janssen)* Zanubrutinib *(Beigene)*	**EML indication** Ibrutinib has been included 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.[131] Ibrutinib was also one of the drugs that the WHO Expert Committee specifically called on MPP to explore licensing. Zanubrutinib was submitted for inclusion in the EML for the management of relapsed/refractory CLL, as well as relapsed/refractory mantle cell lymphoma. The WHO 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 WHO Expert Committee also recommended that MPP explore licensing possibilities for zanubrutinib. **Clinical Relevance** CLL/SLL is the most common form of leukaemia in Western countries (40% of new cases). An estimated 90,600 cases were estimated to have occurred globally in 2017. While age-adjusted death rates have decreased over time in high-income regions, Central Sub-Saharan Africa, East Asia, and Southeast Asia have seen an increase in the same over time. Ibrutinib is the first molecule of its class and has shown to be effective in increasing overall survival and progression free survival. In terms of absolute effect, the use of ibrutinib prolongs progression free survival by at least 50 months (approximately 4 years), which is a relatively large effect in comparison with targeted therapies for other cancers.[132] Zanubrutinib is a next-generation, highly potent, selective, Bruton tyrosine kinase (BTK) inhibitor, which shows 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). **Access** Ibrutinib has been filed for registrations/registered in, among others, six high-burden LMICs.[133] There are limited details on access plans in LMICs. **Patent Status in LMICs** The primary patent on ibrutinib expires in 2026 The primary patent on zanubrutinib expires in 2034
Transduction inhibitor	
Nilotinib *(Novartis)*	**EML indication** Nilotinib has been included in the EML since 2017 for the management of chronic myeloid leukemia, both in children and in adults. **Clinical relevance** In 2017 there was an estimated 34,200 cases of CML. Interestingly, while age-adjusted incidence of CML is decreasing in high social development index (SDI) countries, it has been increasing in low-SDI countries since 1990.[134] Nilotinib has been found to be relatively safe and offered significant therapeutic benefits in cases of CML which were found to be resistant to treatment with imatinib.

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

131 https://www.who.int/publications/i/item/9789240041134

132 https://cdn.who.int/media/docs/default-source/essential-medicines/2021-eml-expert-committee/applications-for-addition-of-new-medicines/a.19_ibrutinib.pdf?sfvrsn=9a1a2c52_4

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

134 https://ehoonline.biomedcentral.com/articles/10.1186/s40164-020-00185-z

PRODUCT *Originator(s)*	MPP ASSESSMENT
Nilotinib *(Novartis)*	**Access** With respect to nilotinib, Novartis and The Max Foundation are collaborating on patient-centered access model delivering free care and treatment, including nilotinib, to people living with CML in nearly 70 LMICs.[135,136] **Patent Status in LMICs** The primary patent on nilotinib expires in 2023.
Androgen receptor inhibitor	
Enzalutamide *(Pfizer, Astellas)*	**EML indication** 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. **Clinical Relevance** Prostate cancer is the second most common cancer in men and is the most common cancer among men in sub-Saharan Africa.[137] In 2020, approximately 1.4 million men globally were diagnosed with prostate cancer. 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. While prostate cancer generally has a favorable prognosis if identified and treated early, some patients will relapse, developing castration resistant prostate cancer (CRPC). At the CRPC stage, the disease is no longer responsive to androgen deprivation therapy (ADT). 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 Hong Kong, South Africa, Brazil, and other countries to bridge the gap between the products' commercial list price and customers' affordability thresholds in order to achieve reimbursement and/or patient access. However, these schemes are not standardised across countries, and it is not clear how many countries are included.[138] According to our consultations with countries, access is still challenging in South Africa where enzalutamide is too expensive to be considered for the inclusion in the National Essential Medicines List. As such, it cannot be provided in the public health sectors that provide cancer care to more than 80% of the population. In India, where the patent application on the compound was refused by the patent office in 2016, several generic manufacturers are producing and distributing generic versions of enzalutamide leading to considerable price rationalisation.[139] **Patent Status in LMICs** The primary patent on the drug expires in 2027, but has been filed or granted in very few LMICs, namely India, Indonesia and South Africa. In India the patent was rejected and the originator appealed the refusal decision by the patent office. The patent is currently under examination so it is uncertain whether generic manufacturers will continue selling the generic version of the drug.
Immune check-point inhibitors	
Multiple *(Multiple)*	**Clinical Relevance** Two ICIs, nivolumab and pembrolizumab, were listed in the WHO EML in 2019 for the treatment of melanoma of the skin. Multiple ICIs were submitted to the WHO EML in 2021 for non-small cell lung cancer (pembrolizumab with nivolumab, atezolizumab, durvalumab as therapeutic alternatives). Immune checkpoint inhibitor therapy has become part of the standard treatment of patients with advanced and metastatic NSCLC in many high-income settings, based on favorable improvements in clinical outcomes. Immune checkpoint inhibitors are associated with a relevant survival benefit well over the established EML threshold for survival (i.e., 4 to 6 months) as first-line treatment in several single studies. The benefit from the checkpoint inhibitors was mostly restricted to patients with PD-L1-positive tumours. Addition of immune checkpoint inhibitors to conventional chemotherapy was associated with a modest increase in toxicity, which may require highly specialised management in selected cases.[140]

135 https://www.themaxfoundation.org/

136 https://www.novartis.com/esg/access/donations

137 https://canceratlas.cancer.org/the-burden/sub-saharan-africa/

138 https://accesstomedicinefoundation.org/publications/improving-access-to-cancer-care-a-first-analysis-of-pharmaceutical-company-actions-in-low-and-middle-income-countries

139 https://economictimes.indiatimes.com/industry/healthcare/biotech/pharmaceuticals/zydus-cadila-launches-generic-prostate-cancer-drug-at-nearly-70-less-price-in-india/articleshow/75623912.cms?from=mdr

140 Park Y-J, Kuen D-S, Chung Y. Future prospects of immune checkpoint blockade in cancer: from response prediction to overcoming resistance. Exp Mol Med. 2018;50(8):109.

PRODUCT *Originator(s)*	MPP ASSESSMENT
Multiple *(Multiple)*	The Committee recognized the important role of immune checkpoint inhibitors as a therapeutic class in the treatment of NSCLC and would welcome a comprehensive review of all available immune checkpoint inhibitors used in the treatment of NSCLC, providing data on duration of therapy, for consideration by the Expert Committee in 2023.[141] Tislelizumab was submitted for consideration for locally advanced or metastatic urothelial cancer and refractory/relapsed Hodgkin Lymphoma. The Committee considered that both applications were premature, with safety and efficacy data (early phase data with small patient numbers and short follow-up), its high price and unknown cost–effectiveness. The Committee advised that it would welcome an application, with more mature data, and including all immune checkpoint inhibitors used in the treatment of urothelial cancer for future consideration. The Committee also considered that immune checkpoint inhibitors could be flagged to the Medicines Patent Pool as candidates for consideration for negotiating public health-oriented licences, noting that negotiating such licences can take some time. The outcome of negotiations might provide important insight for future EML consideration on potential accessibility of this class of medicines in low- and middle-income countries. In response to the WHO EML recommendation, and in light of the expansion of MPP's mandate being expanded to include biotherapeutics and technology transfer, MPP is currently modifying its prioritisation framework to reflect the specific features of biologics. **Access** Access to ICIs is reported to be extremely low and challenging in LMICs[142]. Some scattered industry-led access programs aim to improve availability and affordability to some ICIs. To our knowledge, at this stage, there is limited information about the effectiveness and long-term sustainability of such initiatives. **Patent Status in LMICs** Pembrolizumab (Merck), atezolizumab (Genetech) and nivolumab (Bristol Myers Squibb) have primary patent protection until 2028, 2029 and 2026, respectively. Durvalumab (AstraZeneca) has primary patent protection until 2030. Tislelizumab (Beigene) has primary patent protection until 2033.

6.2 DIABETES

TABLE 10. MPP PRIORITIES FOR DIABETES

PRODUCT *Originator(s)*	MPP ASSESSMENT
Sodium glucose cotransporter 2 (SGLT2) inhibitors	
Empagliflozin *(Boehringer Ingelheim (BI))* Dapagliflozin *(AstraZeneca)* Canagliflozin *(Janssen)*	**EML indication** 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. **Clinical Relevance** SGLT2 inhibitors have been found to be effective in achieving glycemic control in non-pregnant adults.[143] In addition to glycemic control, recent data has shown significant cardiovascular benefit[144] and renal benefits,[145] including in patients without diabetes. Empagliflozin has been approved to treat adults living with heart failure with or without reduced left-ventricular ejection fraction regardless of diabetes status.[146,147] Dapagliflozin has been approved to treat heart failure in patients with reduced ejection fraction, as well as patients with chronic kidney disease, regardless of diabetes status.[148] Canagliflozin is also approved to reduce the risk of major cardiovascular events and end stage kidney disease in adults with type 2 diabetes.[149]

141 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

142 Fundytus A. et al. Access to cancer medicines deemed essential by oncologists in 82 countries: an international, cross-sectional survey. Lancet Oncol. 2021;22(10):1367-1377.

143 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

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

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

146 https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/204629s026lbl.pdf

147 https://www.boehringer-ingelheim.us/press-release/us-fda-approves-jardiance-empagliflozin-treat-adults-heart-failure-regardless-left#:~:text=and%20INDIANAPOLIS%2C%20February%2024%2C%202022,NYSE%3A%20LLY)%20announced%20today.

148 https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202293s024lbl.pdf

149 https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/204353s033,205879s011lbl.pdf

PRODUCT *Originator(s)*	MPP ASSESSMENT
Empagliflozin *(Boehringer Ingelheim (BI))* Dapagliflozin *(AstraZeneca)* Canagliflozin *(Janssen)*	**Access** Current programmes to sustainably improve access in LMICs are unclear. **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).

6.3 REPRODUCTIVE, MATERNAL, NEW-BORN, CHILD AND ADOLESCENT HEALTH (RMNCAH) - RELATED CONDITIONS

TABLE 11. MPP PRIORITIES IN PREVENTION OF PPH

PRODUCT *Originator(s)*	MPP ASSESSMENT
Heat-stable Carbetocin *(Ferring Pharmaceuticals)*	**EML indication** Carbetocin is included in the EML for Postpartum hemorrhage (PPH), and is recommended in the WHO Guidelines for Prevention of PPH. **Clinical Relevance** Every year, eight million of the 136 million women who gave birth develop post-partum haemorrhage (PPH).[150] Approximately 72,000 women die annually due to post-partum haemorrhage[151], globally, representing about one quarter of maternal deaths. More than 99% of deaths due to PPH are in LMICs. In 2018, WHO updated the Guideline on the Use of Uterotonics 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."[152] The Guidelines Development Group made a context-specific recommendation for carbetocin and recommended its use in contexts where its cost is comparable to other effective uterotonics, noting that the current cost of using carbetocin for PPH prevention was greater than the cost of using other effective uterotonics. While other uterotonics are widely available, they suffer from significant quality challenges. Both oxytocin and ergotamine require refrigeration at 2-8°C from manufacturer to end-user. However, this often is not achieved, as supply chains for procuring essential medicines do not often have the required cold chain equipment, and integration with immunisation cold chains is low. Real-world studies have found that in many cases, oxytocin and ergotamine are of inadequate quality in some LMICs due to degradation from storage in excessive heat, with up to 30 – 40% of samples of oxytocin and up to 75% of ergotamine samples showing insufficient levels of the active pharmaceutical ingredient.[153,154] Ergotamine is also contraindicated in patients with hypertensive disorders (including chronic hypertension or pregnancy-related hypertension, pre-eclampsia or eclampsia), making it less suitable for contexts where routine screening for hypertension disorders is not done/possible. Misoprostol also suffers many of the quality challenges of oxytocin described above, with up to 39% of samples having failed quality tests, due to the presence of a high number of unregulated generics available. **Access** Ferring has an access agreement with WHO to provide carbetocin in the public sector of low income and lower middle-income countries (approximately 90 countries) at a price that is comparable to the price UNFPA currently pays for quality-assured oxytocin).[155,156] This access price however does not include upper middle-income countries, nor the private sector in low- and lower middle-income countries. **Patent Status in LMICs** While the primary patent on carbetocin has expired, there are patent applications pending or granted on the heat-stable formulation in several LMICs, expiring in 2031.

150 http://apps.who.int/iris/bitstream/handle/10665/75411/9789241548502_eng.pdf?sequence=1

151 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)32154-2/fulltext

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

153 Torloni MR, Gomes Freitas C, Kartoglu UH, Metin Gülmezoglu A, Widmer M. Quality of oxytocin available in low- and middle-income countries: a systematic review of the literature. BJOG 2016; 123:2076-86.

154 Torloni MR, Bonet M, Betrán AP, Ribeiro-do-Valle CC, Widmer M. Quality of medicines for life-threatening pregnancy complications in low- and middle-income countries: A systematic review. PLoS One. 2020 Jul 10;15(7):e0236060. doi: 10.1371/journal.pone.0236060. PMID: 32649710; PMCID: PMC7351160.

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

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

6.4 MPP WATCHLIST IN NON-COMMUNICABLE DISEASES

TABLE 12. MPP WATCHLIST IN CANCER

PRODUCT *Originator(s)*	**MPP ASSESSMENT**
Androgen receptor inhibitors	
Darolutamide *(Bayer)* Apalutamide *(Janssen)*	**Indications** Both darolutamide and apalutamide are androgen receptor inhibitors (similar to enzalutamide) Darolutamide is currently approved for non-metastatic castration resistant prostate cancer, however recent data shows a reduction in mortality by 32.5% (hazard ratio 0.68; 95% confidence interval, 0.57 to 0.80).[157] Apalutamide is indicated for metastatic and non-metastatic castration resistant prostate cancer. **Clinical relevance** Darolutamide is associated with benefits in overall survival, time to pain progression, time to cytotoxic chemotherapy as well as time to symptomatic skeletal event compared to placebo + other androgen deprivation therapy (ADT) in non-metastatic[158] and metastatic disease.[159] (ESMO MCBS =3, however this has not been updated following recent data) Apalutamide showed improved progression-free survival and overall survival at 24 months compared to placebo + other androgen deprivation therapy.[160] Addition of apalutamide to ADT also showed improved quality of life, compared to ADT+ placebo.[161] (ESMO MCBS = 4). **Patent status in LMICs** Primary patent expiry for darolutamide 2030; and for apalutamide 2027
Oral chemotherapy	
Oral paclitaxel / encequidar, oral docetaxel / encequidar *(Athenex)*	**EML indications** The IV formulations of paclitaxel and docetaxel are on the EML, indicated for multiple solid tumors. The oral formulations are currently under study for metastatic breast cancer (both) and metastatic prostate cancer (docetaxel) **Clinical performance** Paclitaxel: studies have found objective response rate than IV paclitaxel (35.8% for oral versus 23.4% for IV) and increased overall survival (27.9 months for oral paclitaxel + encequidar vs 16.9 months for IV paclitaxel) (analysis ongoing)[162] however, the FDA raised concerns on the increase in neutropenia-related sequelae associated with oral paclitaxel/encequidar, as well as some aspects of the study design.[163] Docetaxel has shown to be well-tolerated, and have acceptable bioavailability, PK characteristics similar to IV formulation.[164] As both drugs are oral formulations, they provide ease of administration. Further, the IV formulations are indicated for multiple solid tumors and included in the EML – the potential of multiple indications and lack of extra diagnostics makes these drugs particularly suited for the LMIC context. **Patent status in LMICs** Formulation patent expiry for oral paclitaxel is in 2036; whereas formulation patent for oral docetaxel expires in 2029.
Third generation Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Receptor Inhibitor (TKI)	
Aumolertinib *(Hansoh Pharma)* Lazertinib *(Janssen)* Furmonertinib *(Allist Pharmaceuticals)*	**Indication** For treatment of epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) (same drug class as osimertinib) **Clinical performance** Aumolertinib is approved in China for treatment of EGFR mutant NSCLC. Phase 3 data shows increased progression free survival, duration of response compared to gefitinib.[165] Lazertinib is approved for treatment of EGFR mutant NSCLC in Korea. It has shown tolerable safety profile and promising clinical activity in patients with NSCLC progressing on or after previous EGFR TKI therapy.[166] Furmonertinib is approved in China for acceptable clinical and safety profiles in patients with NSCLC after previous EGFR TKI therapy. [167]

157 https://www.nejm.org/doi/full/10.1056/NEJMoa2119115
158 https://www.nejm.org/doi/full/10.1056/NEJMoa1815671
159 https://www.nejm.org/doi/full/10.1056/NEJMoa2119115
160 https://www.nejm.org/doi/full/10.1056/NEJMoa1903307
161 https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(19)30620-5/fulltext
162 https://aacrjournals.org/cancerres/article/80/4_Supplement/GS6-01/646066/Abstract-GS6-01-Oral-paclitaxel-with-encequidar
163 https://ir.athenex.com/news-releases/news-release-details/athenex-receives-fda-complete-response-letter-oral-paclitaxel
164 https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.5050
165 https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.9013
166 https://pubmed.ncbi.nlm.nih.gov/31587882/
167 https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30455-0/fulltext

PRODUCT *Originator(s)*	MPP ASSESSMENT
Aumolertinib *(Hansoh Pharma)* Lazertinib *(Janssen)* Furmonertinib *(Allist Pharmaceuticals)*	**Access in LMICs** Aumolertinib is being developed in partnership with EQRx, a company "committed to developing and delivering important new medicines at lower prices".[168] However, the actual access plans for LMICs are not clear at present. **Patent status in LMICs** Primary patent expiry for aumolertinib is 2035; for Lazertinib is 2035, and for furmonertinib is 2035.
KRAS Inhibitors	
Sotorasib *(Amgen)* Adagrasib *(Mirati)*	**Indications** Treatment of KRAS-mutated non-small cell lung cancer (NSCLC) following prior therapy. **Clinical performance** Sotorasib was granted FDA accelerated approval for the treatment of KRAS G12C mutated NSCLC. Studies found promising objective response rates and duration of response in both previously treated and untreated patients.[169] Adagrasib shows favorable anti-tumor activity and safety profile in pre-treated patients with KRAS mutated NSCLC.[170] Adagrasib is also under study for other KRAS12 mutated tumors, including pancreatic and colorectal cancers.[171,172] **Patent status in LMICs** Primary patent expiry for sotorasib 2038; for adagrasib 2037.

TABLE 13. MPP WATCHLIST IN CARDIOVASCULAR CONDITIONS AND HEMATOLOGY

PRODUCT *Originator(s)*	MPP ASSESSMENT
Voxelotor *(Global Blood Therapeutics)*	**Indications** Voxelotor is indicated for the treatment of sickle cell disease in adults, in pediatric patients ⩾ 4 years. **Clinical performance** Voxelotor is associated with durable reduction in hemolysis - improvement in anemia, indirect bilirubin levels and reticulocyte count.[173,174] As Voxelotor has a different mechanism of action from standard of care (mostly hydroxyurea in LMIC), it can be additive to SoC, or used in refractory cases/intolerance. An estimated 305'000 children are born with SCD each year. 90% of the world's sickle cell population lives in 3 countries - Nigeria, DRC, and India. The global meta-estimate for the birth prevalence of homozygous sickle cell disease was 112 per 100 000 live births (95% CI = 101-123) with a birth prevalence in Africa of 1125 per 100 000 (95% CI = 680.43-1570.54) compared with 43.12 per 100 000 (95% CI = 30.31-55.92) in Europe. Mortality and prevalence are highest in Africa.[175] **Patent status in LMICs** Primary patent expires in 2032.

168 https://www.eqrx.com/press-release/aumolertinib-phase-iii-study-meets-primary-endpoint-in-first-line-treatment-for-patients-with-egfr-mutated-advanced-non-small-cell-lung-cancer/

169 https://www.nejm.org/doi/full/10.1056/NEJMoa2103695

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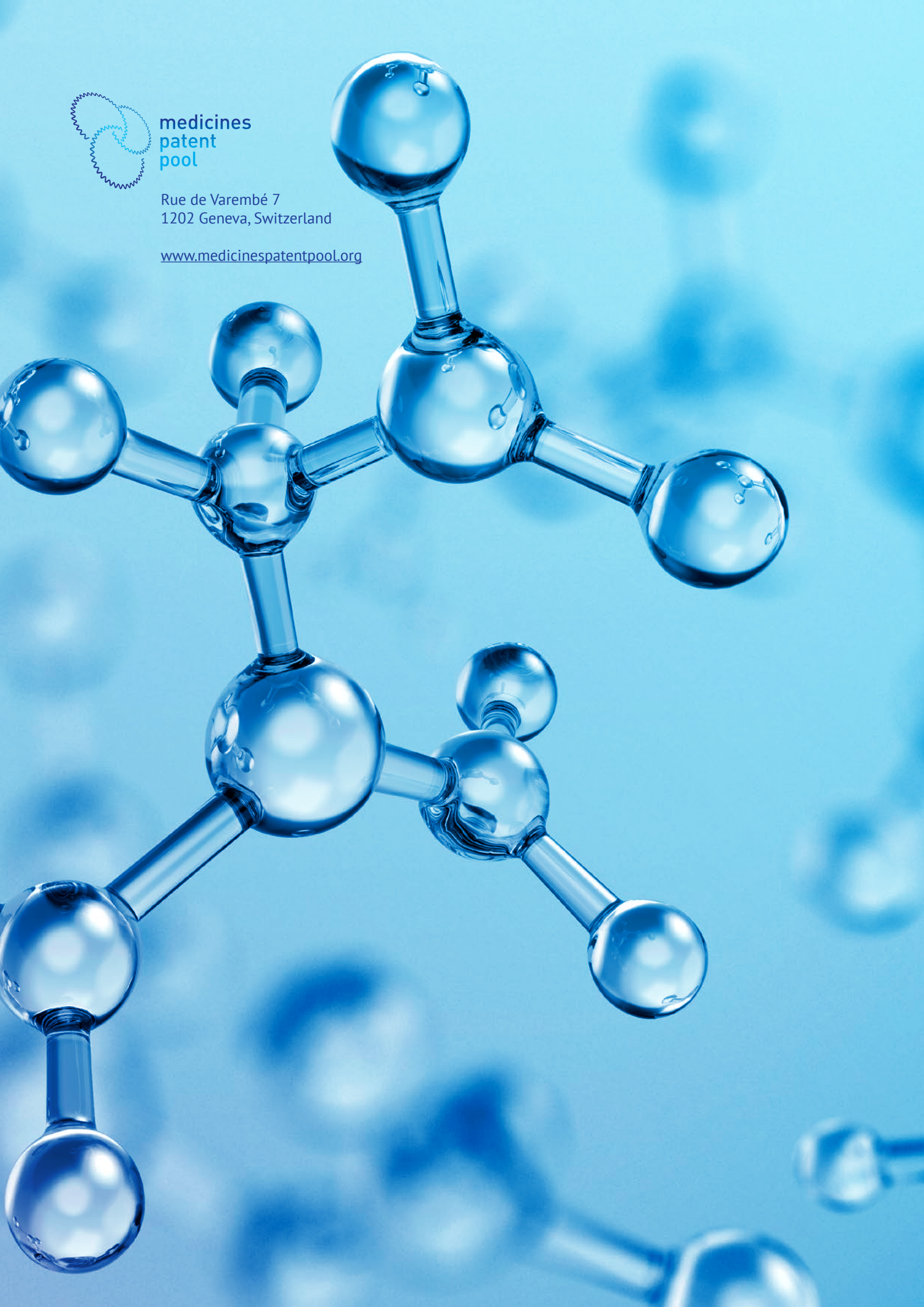

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