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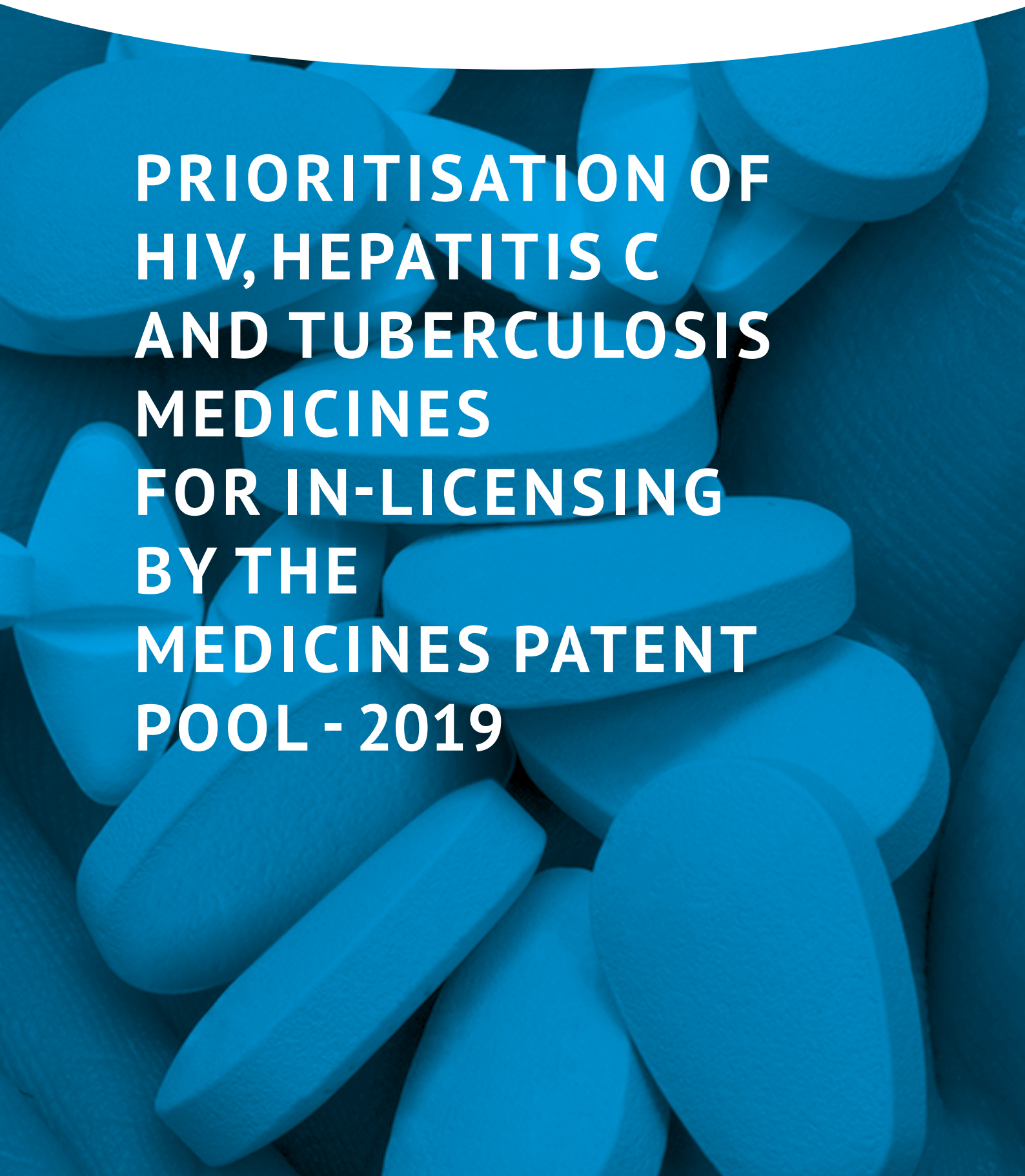

PRIORITISATION OF HIV, HEPATITIS C AND TUBERCULOSIS MEDICINES FOR IN-LICENSING BY THE MEDICINES PATENT POOL - 2019

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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. 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 first step in MPP's work on licensing of HIV, hepatitis C and tuberculosis medicines is selecting possible candidate medicines for in-licensing. This selection is done on an annual basis applying a prioritisation methodology that was developed in 2016 in the context of the MPP's second grant with Unitaid, and further refined in 2017 and 2018.

The objective of the prioritisation is to select candidate medicines for in-licensing that could have the greatest impact for public health in low- and middle-income countries (LMICs). The methodology relies on a thorough review of the medicines on the market as well as those in late-stage development, and consists in an analysis of available clinical data on each medicine, scope and breadth of patent protection, licensing status and market potential. Based on a set of established criteria that were developed following broad consultation with experts, the MPP prioritises a number of medicines on which it then proceeds to seek licences.

In 2019, no changes were made to the prioritisation methodology. In addition to the priorities for in-licensing, we continue to also identify promising new medicines earlier in clinical development that may represent future game-changers, including, for example, medicines with long-acting properties. These are currently being placed in a watch list, as further data from clinical trials would be required for full prioritisation.

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 based on new clinical evidence, changes to WHO recommendations, changes in patent status, evolution in licensing practices and changes in prices or market forecasts for HIV and HCV 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[1].

[1] 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. PRIORITIES IN HIV

TABLE 1 – SUMMARY OF PRIORITY ARVs FOR MPP

ARV	CLASS	MPP ANALYSIS
Cabotegravir long-acting injectable Phase III	Integrase inhibitor	Cabotegravir long-acting injectable (CAB-LAI) is currently in Phase III investigations for treatment maintenance in combination with rilpivirine LAI (RPV-LAI), and separately as a single agent for HIV prevention. CAB-LAI combined with a broadly neutralising antibody VRC01LS will be explored in a new Phase II study as another treatment maintenance option[2]. CAB-LAI given bimonthly holds great potential for the prevention of HIV infection, particularly among key populations for whom adherence to daily oral pre-exposure prophylaxis (PrEP) remains challenging. The need for oral lead-in phase prior to the first injection remains to be elucidated. Importantly, CAB-LAI has a shelf life of 3 years at room temperature[3]. While the combination of CAB-LAI and RPV-LAI could become an option for long-term treatment simplification, the cold chain requirement of the current formulation of RPV-LAI would likely make this regimen less suitable for use in resource-limited settings. The main patent on cabotegravir has been filed or granted in the leading countries of manufacture of ARVs and expires in 2026. In addition, a patent on the long-acting parenteral formulation expires in 2031[4]. The candidate drug has not been licensed for generic production.

The MPP also has a watchlist of promising drug candidates that are in earlier stages of development, such as those outlined in Table 2. While early data suggests that these ARVs have strong potential in LMICs, there is insufficient clinical data at this stage to enable full prioritisation.

TABLE 2 –SUMMARY OF PROMISING ARVs IN EARLY DEVELOPMENT (MPP WATCHLIST)

ARV	CLASS	MPP ANALYSIS
Islatravir (MK-8591, EFdA) Phase II	Nucleoside reverse transcriptase translocation inhibitor (NRTTI)	Islatravir (also known as MK-8591 and EFdA) is a novel NRTTI that, unlike the NRTIs, inhibits the translocation of HIV reverse transcriptase. Characterised by very high potency, islatravir has demonstrated favourable pharmacokinetics as well as long intracellular half-life of its active drug that contribute to the enhanced "forgiveness" of this drug[5]. As a result, islatravir holds great potential in the prevention as well as treatment of HIV, not only as an oral option with the possibility of weekly dosing and/or very low daily dosage, but also as long-acting formulations given every six months or longer[6]. The oral formulation of islatravir is being studied in Phase II in combination with 3TC and DOR as an initial therapy, followed by maintenance with islatravir and DOR only. Long-acting parenteral formulations of islatravir are also under development and have yet to enter human studies[7]. Although there is not yet a paediatric investigation plan in place, islatravir has also been placed on the Watchlist of the WHO Paediatric ARV Drug Optimization Meeting 4 (PADO4) in recognition of its promising long-acting potentials[8]. While the patent on the islatravir molecule has not been filed in LMICs, there are patents pending on the oral or parenteral formulations of islatravir that expire in 2037.

[2] https://clinicaltrials.gov/ct2/show/NCT03739996?cond=VRC01LS&rank=1

[3] Spreen, B (2016) Cabotegravir long-acting injectable nanosuspension, presented at the 17th HIV-HEPPK

[4] MPP-UNITAID (2018), *Intellectual Property Report on Long-Acting Technologies*

[5] Grobler, JA, Fillgrove, KL, and Hazuda, DJ et al (2019) MK-8591 potency and PK provide high inhibitory quotients at low doses QD and QW, presented during CROI, March 4-7, 2019, Seattle

[6] Grobler, J, Friedman, E and Barrett, SE et al (2016) Long-acting oral and parenteral dosing of MK-8591 for HIV treatment or prophylaxis, presented at CROI 2016

[7] https://clinicaltrials.gov/

[8] Paediatric Antiretroviral Drug Optimization (PADO) Meeting 4 - Meeting report – 10-12 December 2018, Geneva, Switzerland: https://www.who.int/hiv/pub/meetingreports/paediatric-arv-optimization-pado4/en/

GSK2838232 (GSK'232) Phase II	Maturation inhibitor	Maturation inhibitors disrupt the HIV life cycle by preventing the formation of mature, infectious viruses. Preliminary data from an ongoing Phase IIa study suggested that GSK'232 – boosted with cobicistat – induced robust virologic response that was unaffected by polymorphism mutations and no gastro-intestinal tolerability issues unlike prior maturation inhibitors[9]. This compound will likely require administration with food[10]. Another maturation inhibitor, GSK3640254, is currently in Phase I/II. Patents on the GSK '232 molecule are expected to expire in 2032.
GS-6207 (GS-CA2) First-in-class Phase I	Capsid inhibitor	Capsid inhibitors are a new class of drugs that function by interfering with the assembly and disassembly of the viral capsids. The drug binds to conserved sites on the capsids, rendering it effective against multiple HIV strains. Additionally, the drug is able to block viral genetic material from entering the host nucleus. GS-6207 is an analog of an earlier candidate, GS-CA1, which was demonstrated to have high potency against all major HIV subtypes as well as mutants resistant to current antiretroviral therapies[11]. Human Phase Ia studies have shown the drug to be safe and well-tolerated following single subcutaneous doses[12]. Sustained delivery supports dosing of at least 3 months, making it attractive for incorporation into long-acting formulations. A Phase Ib study in HIV-infected patients is currently ongoing. Patents on GS-CA2 have been granted or filed in a large number of LMICs, and are expected to expire in 2034-37.

The MPP is also actively monitoring the development of various broadly neutralising antibodies (bNAbs), such as the VRC family and the trispecific bNAb SAR441236. The WHO PADO4 has included bNAbs as a category of interest in its Watchlist[13].

In addition, the MPP continues to monitor other scientific advancements that could shift the paradigm in the prevention, treatment and possible cure of HIV, including novel platform technologies and delivery systems, gene and cell therapies, immunotherapies, and various "shock and kill" strategies[14].

In particular, the MPP is initiating exploratory work on the possible establishment of a collaboration and licensing hub for long acting technologies that could be important to accelerate the development of, and facilitate access to, new long-acting formulations of medicines in HIV, hepatitis C, tuberculosis and malaria that could be of public health importance in LMICs.

Finally, the MPP will continue to monitor the following Phase III and marketed products. This means that while these products have interesting profiles and might become important targets for future licensing by the MPP, some questions on how these products could be utilised in public health settings to meet the treatment and/or prevention needs in developing countries remain to be clarified.

[9] DeJesus, E, Harward, S and Jewell, RC et al (2019) A Phase IIa study of a novel maturation inhibitor GSK2838232 in HIV patients, presented during CROI, March 4-7, 2019, Seattle

[10] Johnson, M, Jewell, RC and Peppercorn, A et al (2017) Early Safety, Tolerability and Pharmacokinetic Profile of GSK2838232, a Novel 2nd Generation HIV Maturation Inhibitor, as Assessed in Healthy Subjects, presented at the 18th International Workshop on Clinical Pharmacology of Antiviral Therapy

[11] Tse, WC, Link, JO, Mulato, A et al (2017) Discovery Of Novel Potent HIV Capsid Inhibitors With Long-Acting Potential, presented at CROI 2017

[12] Eager, JE, Begley, R, Rhee, M et al (2019) Safety And PK Of Subcutaneous GS-6207, A Novel HIV-1 Capsid Inhibitor, presented at CROI 2019

[13] Paediatric Antiretroviral Drug Optimization (PADO) Meeting 4 - Meeting report – 10-12 December 2018, Geneva, Switzerland: https://www.who.int/hiv/pub/meetingreports/paediatric-arv-optimization-pado4/en/

[14] Darcis, G, Driessche, BV and Lin, CA (2017) HIV latency: should we shock or lock? *Trends in Immunology*, 38(3): 217 – 228.

TABLE 3 –SUMMARY OF RECENTLY APPROVED ARVS OR ARVs TO BE FURTHER MONITORED

ARV	CLASS	MPP ANALYSIS
Doravirine *Approved by the FDA in Aug 2018*	Non-nucleoside reverse-transcriptase inhibitor (NNRTI)	Doravirine (DOR) was approved in August 2018 in combination with tenofovir and lamivudine. It is a new-generation NNRTI anticipated to be effective against a broad panel of NNRTI-resistant viruses, though it has not yet been studied in treatment-experienced patients. At a daily dose of 100mg, DOR has been shown to be as effective as efavirenz or boosted darunavir as part of an initial therapy, with improved safety and tolerability[15]. However, DOR is contraindicated with rifampicin and rifapentine, which are important WHO-recommended TB medicines. Additional data, particularly in treatment-experienced patients, will be required to inform the best suited application of this novel NNRTI in a public health setting in developing countries. DOR is currently being studied in adolescents aged 12-17 in a Phase II study, and the agreed paediatric investigation plan covers children from birth and plan for developing granule formulation[16]. DOR is also being studied in combination with Islatravir (MK-8591, EFdA), a promising pipeline medicine currently in Phase II (more below). DOR has also been placed on the Watchlist of the WHO Paediatric ARV Drug Optimization Meeting 4 (PADO4)[17]. Patents on DOR are expected to expire in 2031 and have not been licensed for generic production.
Fostemsavir *Phase III*	Attachment inhibitor	Fostemsavir (FOS) is the oral prodrug of temsavir, a first-in-class attachment inhibitor that targets the HIV envelop protein gp120, therefore blocking the initial interaction between HIV and the host cell. FOS is effective regardless of HIV tropism. Week 48 results from the ongoing Phase III study showed that FOS achieved favourable virologic and immune response III in heavily treatment experienced patients[18]. Although the clinical impact of gp120 diversity and implication in clinical cutoffs (if any) for use of FOS remain to be elucidated[19], FOS could be an important asset for HIV salvage therapies, with potential immune benefits[20]. Patents on FOS are expected to expire in 2025 and the candidate drug has not been licensed for generic production.
Rilpivirine Long-acting injectable	NNRTI	Rilpivirine long-acting injectable (RPV-LAI) is currently in Phase III investigations for treatment maintenance in combination with CAB-LAI. While the combination of CAB-LAI and RPV-LAI could be an option for long-term treatment simplification, the cold chain requirement of the current formulation of RPV-LAI could make this regimen less suitable for use in resource-limited settings. The MPP will continue to monitor the progress with RPV-LAI formulations. Further, the lack of tenofovir in a maintenance strategy makes it difficult to implement in LMICs where HBV co-infections often remain undetected. Patents on rilpivirine expire in 2022/25 and on the injectable formulation in 2026/27. Licences have been granted to several generic manufacturers for the oral formulation, but generic products are not yet on the market.

[15] Querica, R, Slater, A and Clark A et al (2019) Week 48 safety and efficacy of the HIV-1 attachment inhibitor prodrug fostemsavir in heavily treatment-experienced women in the BRIGHTE study, presented during CROI, March 4-7, 2019, Seattle

[16] European Medicines Agency Decision (P/0115/2017) on the acceptance of a modification of an agreed paediatric investigation plan for doravirine in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council. Available from: 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

[17] Paediatric Antiretroviral Drug Optimization (PADO) Meeting 4 - Meeting report – 10-12 December 2018, Geneva, Switzerland: https://www.who.int/hiv/pub/meetingreports/paediatric-arv-optimization-pado4/en/

[18] Querica, R, Slater, A and Clark A et al (2019) Week 48 safety and efficacy of the HIV-1 attachment inhibitor prodrug fostemsavir in heavily treatment-experienced women in the BRIGHTE study, presented during CROI, March 4-7, 2019, Seattle

[19] Lataillade, M, Zhou, N and Roshi, SR et al (2017) Viral drug resistance through 48 weeks, in a Phase 2b, randomized, controlled trial of the HIV-1 attachment inhibitor prodrug, fostemsavir. JAIDS, 77(3): 299-307

[20] Ballana, E and Este, JA (2015) BMS-663068, a safe and effective HIV-1 attachment inhibitor. Lancet HIV, 2(10): e404-e405

3. PRIORITIES IN HEPATITIS C

The hepatitis C regimen prioritised for MPP licensing in 2018, namely glecaprevir/pibrentasvir (or "G/P"), was licensed to the MPP in November 2018. G/P is a once-daily, pan-genotypic combination regimen recommended by the WHO. All other pan-genotypic regimens recommended by the WHO already have licences in place. And all candidate drugs that were previously in phase 2 clinical development have been discontinued by their sponsors. As a result, there are currently no regimens prioritised for in-licensing by the MPP.

Nevertheless, the MPP may explore collaboration with entities working on the possible reformulation of G/P as a long acting formulation which could contribute to the development of a single-dose cure for hepatitis C[21].

4. PRIORITIES IN TUBERCULOSIS

In 2018, three medicines had been identified as possible priorities for in-licensing by the MPP: bedaquiline, delamanid and pretomanid.

An exclusive licence (between Otsuka and Mylan) on delamanid precludes the possibility of the MPP obtaining a licence, at least during the time during which the exclusivity is in place. As a result, delamanid has been dropped from the list of MPP priorities.

Pretomanid has limited IP protection in LMICs, with the compound patent having expired and patents on the combination with bedaquiline and linezolid still pending. Moreover, the patent holder is the TB Alliance, a public health product development partnership, which has already expressed its intention to enter into licensing agreements with generic manufacturers[22]. At this stage, therefore, there does not appear to be a public health need for the MPP to become involved in the licensing of pretomanid.

As a result, only one priority for in-licensing by the MPP remains, namely bedaquiline. The recent update of the WHO guidelines making bedaquiline one of four medicines to be included in the all-oral longer MDR-TB regimens, has increased the importance of bedaquiline for treatment of MDR-TB in LMICs. As a result, bedaquiline continues to be a priority for MPP licensing.

[21] https://unitaid.org/assets/Unitaid-LA-compendium-November-2018-for-UTD-web-converted.pdf

[22] https://www.tballiance.org/news/pretomanid-enters-FDA-review

TABLE 4 –SUMMARY OF PRIORITY TB DRUGS FOR MPP

TB DRUG	CLASS	MPP ANALYSIS
Bedaquiline *Phase III ongoing* *Registered with the US FDA and EMA*	Diarylquinoline	In 2019, the new WHO Consolidated Guidelines on Drug-Resistant Tuberculosis recommended bedaquiline (BDQ) as one of four medicines to be used as part of the all-oral longer regimen in adult MDR-TB patients[23]. BDQ is also included in a number of new regimen trials for both Drug Resistant TB (DR-TB) and Drug Sensitive TB (DS-TB), including STREAM 2 (official phase III trial) endTB, PRACTECAL, NiXTB, NeXT and ZeNix[24]. In 2019, the TB Alliance submitted to the USFDA for approval a new regimen comprising bedaquiline, pretomanid and linezolid for the treatment of extensively drug-resistant (XDR) TB. BDQ has been the subject of a donation program that has facilitated its introduction in 64 countries. Following the end of the donation program in March 2019, the GDF has announced a price of USD 400 for a course of bedaquiline for all countries who can purchase medicines via GDF[25]. The compound patent on BDQ is expected to expire around 2023, with secondary patents expiring in 2025 and 2027. A licence has been granted to one company for the manufacture and supply of BDQ in Russia and a number of other countries in that region[26]. An MPP licence with a broader geographical scope under public health-oriented terms and conditions could contribute to making the product available at affordable prices.

In addition, a number of TB candidate medicines have now proceeded to phase II. They are mentioned below as part of a watchlist in TB. Insufficient data is currently available for the full prioritisation of these compounds.

TABLE 5 –SUMMARY OF TB COMPOUNDS PHASE II DEVELOPMENT (MPP WATCHLIST)

TB DRUG CANDIDATE	CLASS	MPP ANALYSIS
Telacebec (Q203)	Imidazopyridine amide	This compound has completed enrolment in a Phase IIa, open-label, randomised study in treatment-naïve, sputum smear-positive patients with drug-sensitive pulmonary TB[27]. Similar to bedaquiline, it functions by inhibiting energy metabolism, although it is thought that the two drugs could work synergistically[28].
Delpazolid (LCB01-0371)	Oxazolidinone	Delpazolid is a new oxazolidinone with cyclic amidrazone synthesised by LegoChem BioSciences Inc. Currently recruiting for a phase II trial to evaluate early bactericidal activity, safety and pharmacokinetics[29].
OPC-167832	3,4-dihydrocarbostyril derivative	This compound is being developed in a phase 1/2 trial of multiple oral doses of OPC-167832 for uncomplicated pulmonary tuberculosis by Otsuka, in collaboration with the Bill and Melinda Gates Foundation[30].

[23] WHO, WHO Consolidated Guidelines on Drug-Resistant Tuberculosis

[24] DR-TB Clinical Trials Progress Report: RESIST TB: http://www.resisttb.org/?page_id=1602 (Accessed 12th March 2018)

[25] http://www.stoptb.org/gdf/drugsupply/bedaquiline.asp

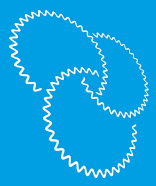
[26] https://www.janssen.com/janssen-broadens-collaboration-russias-pharmstandard-advance-ongoing-efforts-tackle-multi-drug

[27] https://www.newtbdrugs.org/pipeline/trials/phase-2-telacebec-q203-eba

[28] http://www.pipelinereport.org/2017/tbtx

[29] https://clinicaltrials.gov/ct2/show/NCT02836483

[30] https://clinicaltrials.gov/ct2/show/NCT03678688?term=167832&rank=1



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