



The Medicines Patent Pool Foundation

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

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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 and health technologies 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 to assess products of potential interest in all health areas and all stages of clinical development. In line with MPP's current mandate, products assessed now also include biologics and novel medical technologies. This mechanism contributes to ensuring MPP focuses its efforts on medicines for which licensing could have the greatest public health impact.

MPP's prioritisation process generates lists of patented medicines for which expanded access in LMICs could provide significant health benefits over standards of care, and where voluntary licensing through MPP could lead to substantial public health impact. Three lists are generated:

Priority Lists:

List A: A priority list for SRA-approved products, products included in WHO guidelines and products with sufficient clinical data supporting its inclusion in the list of candidates that MPP pursues for in-licensing.

For a product to be included in List A, there should be evidence that it provides advantages compared to the standard of care (e.g., better tolerability, higher safety profile, easier administration route, higher efficacy, etc.).

List B: A priority list of investigational products for which supporting data is still being generated but there are indicators of significant benefits and substantial public health impact with an MPP intervention, that might be amplified if the agreement is concluded earlier in the product life cycle. The approach of the MPP in relation to products in List B is not only to support access to future products, but also to facilitate their further development.

Watchlist:

A watchlist of SRA-approved and investigational products for which supporting data is still lacking and/or key challenges still need to be addressed before obtaining clarity on the significance of an MPP intervention. Products in the watchlist are closely monitored but MPP negotiations with patent holders are not triggered by this inclusion.

These lists are evidence-based and guided by MPP's prioritisation framework. They are reassessed and complemented once yearly 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. This yearly update is undertaken after consultations with MPP's scientific and community advisory panels (SAP and CAP respectively), posted on MPP website and available publicly.

2 Prioritisation framework

In order to guide products assessment, the framework addresses the following considerations:

- Does the product address a public health need?
- Are there any access hurdles (anticipated or existing) for the product in low-and-middle-income countries, including in relation to intellectual property?
- What would be the effect of MPP intervention on access?

By addressing these questions, MPP collects insights about public health and access dimensions of the products assessed.

The lists resulting from the prioritisation carried out in early 2023 for several health areas is provided below, as well as the rationale behind this listing.

3 MPP 2023 Lists of Prioritised and watchlist products

Table 1 summarises the contents of the MPP priorities (lists A and B) and watchlist products for 2023.

	Main indication		Drug class		
	Infectious diseases	HIV			
Tuberculosis					
Viral hepatitis					
Non-communicable diseases and conditions	Non-small cell lung cancer	3 rd generation Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Receptor Inhibitor (TKI)	CRAS inhibitors		
	HR+/HER2-advanced breast cancer	Cyclin-dependent kinase (CDK) 4/6 inhibitors			
	HER2-overexpressing breast cancer	mAb			
	Chronic lymphocytic leukemia	Bruton's tyrosine kinase inhibitors			
	Castration-resistant Prostate cancer	Androgen receptor inhibitor			
	Multiple indications in Oncology	Immune check-point inhibitors			
		Oral chemotherapy			
	Diabetes, cardiovascular and metabolic disorders and conditions	Sodium glucose cotransporter 2 (SGLT2) inhibitors			
	Reproductive, maternal, new-born and child health (RMNCH) and haematological disorders	Prevention of post-partum haemorrhage			
		Sickle cell disease			

Priorities			
List A		List B	
Product	Originator	Product	Originator
Lenacapavir	Gilead Sciences	Islatravir	Merck
		Ultra-long-acting injectable formulation for ARVs	University of North Carolina at Chapel Hill
Bedaquiline	Janssen	Quabodepistat	Otsuka
-	-	-	-
Osimertinib	AstraZeneca	Aumolertinib	Pharma/EQRx
-	-	-	-
Ribociclib	Novartis	-	-
Abemaciclib	Eli Lilly	-	-
Ibrutinib	Pharmacyclis (AbbVie)/ Janssen	-	-
Zanubrutinib	Beigene	-	-
-	-	-	-
PD-1/PD-L1 inhibitors	Multiple	-	-
-	-	--	
Empagliflozin	Boehringer Ingelheim	-	-
Canagliflozin	Janssen	-	-
Heat-stable carbetocin	Ferring Pharmaceuticals	-	-
-	-	-	-

Watchlist	
Product	Originator
Doravirine	MSD
GSK3640254	ViiV Healthcare
Cabotegravir	ViiV Healthcare
Rilpivirine	Janssen
Three-monthly dual vaginal ring for HIV PrEP and prevention of unintended pregnancy	The Population Council
BTZ-043	University of Munich and the German Center for Infection Research
Delpazolid	LegoChem BioSciences
GSK 3036656	GlaxoSmithKline
Macozinone	Swiss Federal Institute of Technology Lausanne (EPFL)
Telacebec	Qurient Co. Ltd
Fobrepodacin	Spero Therapeutics, LLC, Bill & Melinda Gates Medical Research Institute
Sudapyridine	Shanghai Jiatan Biotech
Bulevirtide	Gilead
Lazertinib	Janssen
Furmonertinib	Allist Pharmaceuticals
Adagrasib	Mirati
Sotorasib	Amgen
-	-
Trastuzumab subcutaneous	Roche
-	-
Enzalutamide	Pfizer/Astellas
Darolutamide	Bayer
Apalutamide	Janssen
-	-
Oral paclitaxel / encequidar	Athenex
Oral docetaxel / encequidar	
-	-
-	-
Voxelotor	Global Blood Therapeutics

Table 1- MPP prioritisation lists 2023.

Table 2 below summarises the main changes in the list compared to 2022 prioritisation. There were additions, changes in classification, and products that do not appear in the lists anymore:

Additions: Eight products are added to MPP’s priorities and watchlist as follows:

- Four products approved/investigated for HIV treatment and/or prevention:
 - o Islatravir in the priorities (list B)
 - o Ultra-long-acting injectable formulation for ARVs in the priorities (list B)
 - o Cabotegravir long-acting for HIV treatment (as part of a wider regimen) in the watchlist.
 - o Three monthly 90-day dual vaginal ring for HIV PrEP and prevention of unintended pregnancy (watchlist)
- Two products for TB treatment: Fobrepodacin and Sudapyridine were added to the watchlist.
- One product for viral hepatitis treatment: Bulevirtide was added to the watchlist.
- One product for breast cancer: Trastuzumab subcutaneous was added to the watchlist.

Changes: Three products were moved within the lists:

- Quabodepistat (OPC-167832), a product investigated for tuberculosis treatment, was previously in the watchlist and is now considered a list B priority.
- Aumolertinib, an EGFR TKI used in non-small cell lung cancer was moved from the watchlist to list B priority.
- Enzalutamide, an androgen receptor antagonist used in prostate cancer was moved from list A to the watchlist.

Deletions: Five products were removed from the prioritisation list as follows:

- Dapagliflozin, a sodium glucose cotransporter 2 inhibitor (SGLT2i) was deleted from the priority list as its compound patent expires in 2023¹.
- Palbociclib, a CDK 4/6 inhibitor was deleted from the priority list as its compound patent expires in 2023².
- It should be also noted that MPP does not include in its prioritisation medicines for which it has already obtained licences in the past³. In 2022, MPP entered into voluntary licence agreements for three of its prioritised products, that consequently do not appear in the list anymore (Cabotegravir LA for HIV PrEP, Nilotinib for chronic myeloid leukemia and BEPO® technology for malaria vector control.)

Additions to the lists		Changes within the lists		Deletions from the lists	
Product	Position	Product	Position	Product	Reason for deletion
Islatravir	List B	Quabodepistat (OPC-167832)	List B	BEPO technology for malaria vector control ⁴	Licence signed
Ultra-long-acting injectable formulation for ARVs	List B	Aumolertinib	List B	Nilotinib to treat chronic myeloid leukaemia ⁵	Licence signed
Cabotegravir LA as HIV treatment component	Watchlist	Enzalutamide	Watchlist	Cabotegravir LA for HIV PrEP ⁶	Licence signed
Three monthly dual vaginal ring for HIV PrEP and prevention of unintended pregnancy	Watchlist	-	-	Dapagliflozin	Main patent expiring in 2023
Fobrepodacin	Watchlist	-	-	Palbociclib	Main patent expiring in 2023
Sudapyridine	Watchlist	-	-	-	-
Bulevirtide	Watchlist	-	-	-	-
Trastuzumab subcutaneous	Watchlist	-	-	-	-

1 <https://www.medsdal.org/?product%5B%5D=Dapagliflozin+10+mg&product%5B%5D=Dapagliflozin+5+mg&page=1>

2 <https://www.medsdal.org/?keywords=palbociclib&page=1>

3 <https://medicinespatentpool.org/progress-achievements/licences>

4 <https://medicinespatentpool.org/licence-post/long-acting-technology-for-malaria-vector-control>

5 <https://medicinespatentpool.org/licence-post/nilotinib>

6 <https://medicinespatentpool.org/licence-post/cabotegravir-long-acting-la-for-hiv-pre-exposure-prophylaxis-prep>

The next sections 4 to 7 provide an overview of the prioritised and watchlist medicines in all health areas that were assessed. Then, section 8 provides detailed evaluations of all products. When publicly available, access information is also indicated. However, for many of the medicines listed, information on current access programmes is limited. As such the assessment focuses on clinical and public health significance, as well as patent status.

4 Infectious diseases and conditions

4.1 HIV: Overview of MPP priorities and watchlist

This chapter provides a summary of MPP priorities and watchlist respectively, in the field of HIV. A short rationale, supporting their inclusion in either the priority list or the watchlist is provided. Three HIV medicines (or investigational treatments/prevention tools) are identified as priorities and five are included in the watchlist.

- **Priorities:**

- **Lenacapavir:** lenacapavir continues to be a priority for MPP. Lenacapavir was first included as a priority in 2022 and it continues to be a priority (List A) because its new mechanism of action and the long-acting properties (6 months dosing interval) will likely make it an important product in HIV prevention and/or treatment (in combination with other medicines). The clinical programs continue to show favourable efficacy and safety profile. Furthermore, lenacapavir has been prioritised by both PADO and CADO ⁷.

[full assessment here](#)

- **Islatravir:** islatravir was deprioritised in the 2022 report because of safety concerns, which had led to clinical trials being put on hold. Merck has recently resumed islatravir's development program using a lower dose of islatravir but questions on the long-term safety remain. Islatravir's new mechanism of action and its long-acting properties have the potential to make it an important product in HIV treatment. Furthermore, islatravir is one of the most promising drugs studied in combination with lenacapavir and it is used as an active ingredient co-formulated with several long-acting technology platforms. For these reasons, it is now listed in the priorities still in development (List B).

[full assessment here](#)

- **Ultra-long-acting injectable formulation for ARVs:** This platform technology offers the ability to integrate multiple drugs into a single formulation that upon injection, releases the medicine(s) over several weeks or months for a systemic drug delivery. It has potential applications in HIV treatment and/or prevention as well as other indications including contraception, in the form of a multipurpose technology (MPT). As it is in pre-clinical development, it was included in priority list B.

[full assessment here](#)

- **Watchlist:**

- **Doravirine:** doravirine was listed in the previous watchlist. It is developed in combination with islatravir and it has the potential to be an alternative treatment for PLHIV experiencing weight-gain. Additionally, its development program is focused on infants and children, which make doravirine an attractive drug. However, the evidence of clinical benefits over the standard of care is unclear and therefore doravirine is listed in the watchlist.

[full assessment here](#)

⁷ WHO publication: [Priorities for antiretroviral drug optimization in adults and children: report of a CADO PADO and HIVResNet joint meeting \(2022\)](#)

- **GSK3640254:** GSK3640254 was listed in 2022 in the watchlist. It is the most advanced ARV in the HIV maturation inhibitor class. Because of the limited data on its safety and efficacy, it is listed again in the watchlist.
[full assessment here](#)
- **Cabotegravir for HIV treatment** (as part of a wider regimen): cabotegravir was an MPP priority and it was licensed to MPP in 2022 for PrEP only. Cabotegravir is the only INSTI approved, in combination with rilpivirine, as a long-acting regimen for HIV treatment. While rilpivirine cold chain requirement potentially adds challenges to implementation in LMICs, cabotegravir is the only approved long-acting antiretroviral (ARV) belonging to the integrase strand transfer inhibitor (INSTI) class. Long-acting cabotegravir for treatment is now listed on the watchlist, because of its potential of becoming a key component for future long-acting regimens for HIV treatment that could be introduced in LMICs.
[full assessment here](#)
- **Rilpivirine:** rilpivirine was listed in the previous watchlist. Rilpivirine is the only NNRTI approved, in combination with cabotegravir, as a long-acting regimen for HIV treatment. However, rilpivirine cold chain requirements could make it difficult for this drug to be implemented in LMICs. Additionally, it has been reported that rilpivirine could increase the risk for depressive disorders and hepatic adverse effects. Furthermore, rilpivirine resistance would largely exclude future use of the NNRTI class drugs, and therefore it is kept in the watchlist.
[full assessment here](#)
- **Three monthly dual vaginal ring for HIV PrEP and prevention of unintended pregnancy:** This multipurpose intravaginal ring follows the path of the monthly dapivirine ring for HIV prevention, with the added characteristic of preventing unintended pregnancies on top of HIV and with a longer duration of use (three months instead of one). As the product is still in early development stages and the patent barriers are unclear, it was included in the watchlist.
[full assessment here](#)

A detailed description of all the products for HIV (priorities and watchlist) is provided in the last chapter of this report.

4.2 Tuberculosis: Overview of MPP priorities and watchlist

This chapter provides a summary of MPP priorities and watchlist respectively, in the field of TB. A short rationale, supporting their inclusion in either the priority list or the watchlist, is provided. Two TB medicines are identified as priority for in-licensing. Seven other medicines are in MPP watchlist as it is considered that there is currently insufficient clinical data and unclear development plan to prioritise them for licensing at this stage.

- **Priorities:**

- **Bedaquiline:** Bedaquiline was already identified as a priority in the previous prioritisation process, and it remains an essential drug to fight TB, therefore it has been prioritised again (List A).
[full assessment here](#)
- **Quabodepistat:** quabodepistat was listed in the watchlist in the previous prioritisation report. It is now listed in the priorities (List B) because, despite lack of compelling clinical data, it has a new mechanism of action and it is now studied as part of a new, promising, TB regimen under the Project to Accelerate New Treatments for Tuberculosis (PAN-TB) program.
[full assessment here](#)

- **Watchlist:**

- **BTZ-043:** the clinical data on BTZ-043 are still immature and therefore the drug remains in the watchlist.
[full assessment here](#)
- **Delpazolid:** the clinical data on delpazolid are still immature and therefore the drug remains in the watchlist.
[full assessment here](#)
- **GSK3036656:** the clinical data on GSK3036656 are still immature and therefore the drug remains in the watchlist.
[full assessment here](#)
- **Macozinone:** the clinical data on macozinone are still immature and therefore the drug remains in the watchlist.
[full assessment here](#)
- **Telacebec:** the clinical data on telacebec are still immature and therefore the drug remains in the watchlist.
[full assessment here](#)
- **Fobrepodacin:** fobrepodacin was recently added to the watchlist since the clinical hold issued last year was recently lifted. The clinical data on fobrepodacin are still immature and therefore the drug is listed in the watchlist.
[full assessment here](#)
- **Sudapyridine:** sudapyridine was recently added because of its promising development plan and because it could represent an alternative to bedaquiline, an important drug for MDR-TB in the priority list of MPP for several year. The clinical data on sudapyridine are still immature and therefore the drug is listed in the watchlist.
[full assessment here](#)

A detailed description of all the products for TB (priorities and watchlist) is provided in the last chapter of this report.

4.3 Viral hepatitis: Overview of MPP priorities and watchlist

This chapter provides a summary of MPP priorities and watchlist in the field of viral hepatitis. No medicine was identified as priority, but one medicine is now included in the watchlist.

- **Priorities:** No priorities have been identified for 2023
- **Watchlist:**
 - **Bulevirtide:** Bulevirtide was recently conditionally approved by EMA and it is today the only specific treatment for hepatitis delta. However, questions remain about the length of treatment and the formulation requiring a daily injection, which could hamper its use in LMICs. Additionally, its safety and efficacy are still under evaluation and therefore bulevirtide has been included in the watchlist.
[full assessment here](#)

A detailed description of this product is provided in the last chapter of this report.

5 Non-communicable diseases and conditions

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 (NCDs) of public health importance, such as cancer, diabetes, and reproductive, maternal, new-born and 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 above. In line with MPP's expanded mandate to cover biotherapeutics, this report, therefore, also includes biotherapeutics recommended by the WHO EML for MPP to explore, when MPP's assessment indicates that an MPP intervention might increase access to these therapies.

5.1 Overview of MPP priorities and watchlist for oncology

This chapter provides a summary of MPP priorities and watchlist respectively, in the field of oncology. Nine oncology medicines are identified as priorities (lists A and B) and seven are included in the watchlist. Relevant changes in the 2023 MPP prioritisation report compared to the previous year: Nilotinib was removed from the prioritisation report following the signing of a voluntary licensing agreement with Novartis AG in October 2022; Palbociclib was deprioritised as compound patent will expire in 2023; Enzalutamide has been downgraded to the watchlist due to the approaching patent expiry and very limited number of countries where there may be patent challenges to generic market entry ; Aumolertinib was moved from the watchlist to list B and trastuzumab subcutaneous was added to the watchlist.

- **Priorities:**

- **Osimertinib:** A 3rd generation EGFR TKI, osimertinib has demonstrated significant benefits compared to standard first-line treatments of 1st and 2nd generations in the EML for the treatment of NSCLC. Osimertinib is approved by the FDA and the EMA. For these reasons, osimertinib has been prioritised again (List A).
[full assessment here](#)
- **Aumolertinib:** A 3rd generation EGFR TKI, aumolertinib has demonstrated significant benefits compared to standard first-line treatments of 1st and 2nd generations in the EML for the treatment of NSCLC. Aumolertinib is under review for approval by the EMA. For these reasons, it was moved to MPP B list.
[full assessment here](#)
- **Ribociclib:** Ribociclib is an oral CDK4/6 inhibitor, approved by the FDA in 2017. CDK 4/6 inhibitors are the recommended preferred option in the treatment of advanced breast cancer. The EML expert committee recognised its potential for future inclusion and recommended to MPP to explore it for licensing. For these reasons, ribociclib has been prioritised again (List A).
[full assessment here](#)
- **Abemaciclib:** Abemaciclib is oral CDK4/6 inhibitor, approved by the FDA in 2021, recommended as the preferred option in the treatment of advanced breast cancer. CDK 4/6 inhibitors are the recommended preferred option in the treatment of advanced breast cancer. The EML expert committee recognised its potential for future inclusion and recommended to MPP to explore it for

licensing. Abemaciclib has a similar safety profile to Ribociclib but a different dosing regimen making it an alternative of interest. For these reasons, abemaciclib has been prioritised again (List A).

[full assessment here](#)

- **Ibrutinib:** Ibrutinib is a Bruton's tyrosine kinase inhibitor approved by the FDA in 2013 and added to the complimentary list of the EML for the treatment of chronic lymphocytic leukaemia. Ibrutinib demonstrated major benefits compared to chemo-immunotherapy. The EML expert committee recommended to MPP to explore it for licensing. For these reasons, ibrutinib has been prioritised again (List A).

[full assessment here](#)

- **Zanubrutinib:** Zanubrutinib is a Bruton's tyrosine kinase inhibitor (BTKi) approved by the FDA in 2023 for the treatment of chronic lymphocytic leukaemia (CLL). Recognizing the emerging important role of BTKi as a therapeutic class in the treatment of CLL, the EML Committee advised that it would consider an application for Zanubrutinib as therapeutic alternative for inclusion and recommended to MPP to explore it for licensing. For these reasons, zanubrutinib has been prioritised again (List A).

[full assessment here](#)

- **Immune check-point inhibitors:** Multiple immune check-point inhibitors have been approved to treat a variety of cancers. The EML committee recognised their importance as a therapeutic class, two of them were listed on the EML in 2019 for the treatment of skin melanoma and recommended to MPP to explore them as candidates for licensing. For these reasons, the immune check-point inhibitors have been prioritised again (List A).

[full assessment here](#)

- **Watchlist:**

- **Lazertinib:** Lazertinib is a 3rd generation EGFR TKI, pending approval from a recognised stringent registration authority, presenting superiority over the 1st generation of EGFR TKI. Lazertinib has a strong potential as alternative option and therefore has been listed again in the watchlist.

[full assessment here](#)

- **Furmonertinib:** Furmonertinib is a 3rd generation EGFR TKI, has been shown to be highly brain penetrant and was granted Fast Track Designation by the FDA. Furmonertinib has a strong potential as alternative option for NSCLC and therefore has been listed again in the watchlist.

[full assessment here](#)

- **Enzalutamide:** Enzalutamide is a 2nd generation androgen receptor antagonist approved by the FDA in 2012 and added to the complimentary list of the EML in 2021. Enzalutamide is an essential alternative in the treatment landscape for prostate cancer. Enzalutamide has been downgraded to the watchlist due to the approaching patent expiry and very limited number of countries where there may be patent challenges to generic market entry.

[full assessment here](#)

- **Apalutamide:** Apalutamide is a 2nd generation androgen receptor antagonist approved by the FDA in 2018. As a class of drugs, 2nd androgen receptor antagonists improve overall survival in prostate cancer patients. Apalutamide is a strong potential alternative candidate and therefore has been listed again in the watchlist.

[full assessment here](#)

- **Darolutamide:** Darolutamide is a 2nd generation androgen receptor antagonist approved by the FDA in 2019. As a class of drugs, 2nd androgen receptor antagonists improve overall survival in prostate cancer patients. Darolutamide is a strong potential alternative candidate and therefore has been listed again in the watchlist.

[full assessment here](#)

- **Sotorasib:** Sotorasib is an oral KRAS inhibitor, that received accelerated approval by the FDA for the treatment of NSCLC in 2021. A recent study showed that sotorasib offered significant benefits compared to the standard intravenous treatment and therefore sotorasib has been listed again in the watchlist.
[full assessment here](#)
- **Adagrasib:** Adagrasib is an oral KRAS inhibitor, that received approval by the FDA for the treatment of NSCLC in 2022, and showcases durable clinical benefits in patients and therefore has been listed again in the watchlist.
[full assessment here](#)
- **Oral paclitaxel / encequidar - Oral docetaxel / encequidar:** The intravenous formulation of paclitaxel and docetaxel have been added to the EML in 2011 and used since in the treatment protocols for many cancers. This new mode of administration, without new requirement for diagnostics, makes both indications promising for LMIC settings pending their approval by recognised SRA, and therefore have been listed again to the watchlist.
[full assessment here](#)
- **Trastuzumab subcutaneous:** Trastuzumab subcutaneous is a monoclonal antibody approved by the FDA in 2019 for the treatment of HER2-overexpressing breast cancer. It is the same monoclonal antibody as intravenous trastuzumab and can be administered more easily and rapidly. This new mode of administration is promising for LMIC settings and therefore has been added to the watchlist.
[full assessment here](#)

5.2 Overview of MPP priorities for diabetes, cardiovascular and metabolic disorders and conditions

This chapter provides a summary of MPP priorities in the field of diabetes. Two anti-hyperglycaemic medicines are identified as priority.

Relevant change in the 2023 MPP prioritisation report compared to the previous year: Dapagliflozin was deprioritised as its compound patent will expire in 2023.

- **Priorities:**

- **Empagliflozin:** Empagliflozin is an oral hypoglycaemic agent approved by the FDA in 2014 and added to the core list of the EML in 2021 as add-on treatment for adults living with type 2 diabetes. Empagliflozin was selected as the representative of the class of sodium glucose cotransporter 2 (SGLT2) inhibitors. For these reasons, empagliflozin has been prioritised again (List A).
[full assessment here](#)
- **Canagliflozin:** Canagliflozin is another sodium glucose cotransporter 2 (SGLT2) inhibitor, approved by the FDA in 2013 and added to the EML 2021 as a therapeutic alternative to Empagliflozin. For these reasons, it has been prioritised again (List A).
[full assessment here](#)

The EML Committee recommended that MPP explores how to facilitate affordable access to SGLT2 inhibitors in low and middle-income countries through public health-oriented licences with the companies holding the patents.

5.3 Overview of MPP priorities and watchlist for RMNCH and haematological disorders

This chapter provides a summary of MPP priorities in the field of Reproductive, Maternal, New-born and Child Health (RMNCH) and haematological diseases. One medicine is identified as priority for RMNCH, and one is included on the watch list for haematological disease.

- **Priority:**
 - **Heat-stable carbetocin:** Carbetocin was approved by the FDA in 1997 and its heat-stable added to the core list of the EML in 2019 for the prevention of postpartum haemorrhage based on similar effects compared to oxytocin for efficacy and safety outcomes. Heat-stable carbetocin does not require cold chain transport or refrigerated storage thus offering advantages and reducing the risk of quality loss compared to oxytocin in LMICs. Heat-stable carbetocin is promising for LMIC settings and therefore has been prioritised again (List A). [full assessment here](#)

- **Watchlist:**
 - **Voxelotor:** Voxelotor is a haemoglobin oxygen-affinity modulator approved by the FDA in 2019 for the treatment of sickle cell disease. About 90% of the global sickle cell population lives in LMIC. Voxelotor has a different mode of action from that of conventional standard of care therapies, which makes it relevant as additional treatment or in case of intolerance. For these reasons, it has been listed again in the watchlist. [full assessment here](#)

6 Detailed assessments of the products

6.1 Detailed assessment of HIV priorities

In this chapter we provide additional information on the HIV medicines listed as priorities.

6.1.1 Lenacapavir (Gilead Sciences) for treatment and PrEP

Lenacapavir is Gilead's ARV being studied for both HIV treatment and PrEP. Lenacapavir is a small molecule belonging to the capsid inhibitors class ⁸, a new class of drugs that function by interfering with the assembly and disassembly of the viral capsid. Because lenacapavir is a first-in-class ARV, it does not show cross-resistance with other ARV classes ⁹. Its high potency and long half-life make it a suitable candidate for long-acting formulations that can increase adherence and ease pill burden in PLHIV.

Lenacapavir is approved by the FDA, in combination with other antiretroviral(s), for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations ¹⁰. The approval was based on the CAPELLA study showing that 83% patients, at week 52, were virologically suppressed, which suggests that lenacapavir injection every 6 months is effective ¹¹.

Recently, a combination of lenacapavir and two bNABs (teropavimab and zinlirvimab) was shown to sustain viral suppression for 6 months in selected people with HIV ¹². This showcases the possibility of a complete twice-yearly HIV treatment regimen. A follow up phase 2 study is ongoing.

Oral and subcutaneous lenacapavir formulations are also being studied in combination with other oral ARVs (BIC, TAF and FTC) for the treatment of HIV naïve patients (CALIBRATE study) ¹³. The virologic suppression at week 52 was on a par with modern oral first-line therapy studies, however, the results included a small group of patients and further studies are needed ¹⁴. 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 ¹⁵. Lenacapavir is also studied for PrEP in the form of 6-months, stand alone, sub-cutaneous injections, in comparison with TAF/FTC and TDF/FTC, but the results are pending ¹⁶.

Lenacapavir is generally well tolerated and with a promising safety profile, headache and nausea were the most frequent non-injection site reaction adverse events. However, important drug-drug interactions could

8 Link JO, Rhee MS, Tse WC, Zheng J, Somoza JR, Rowe W, Begley R, Chiu A, Mulato A, Hansen D, Singer E, Tsai LK, Bam RA, Chou CH, Canales E, Brizgys G, Zhang JR, Li J, Graupe M, Morganelli P, Liu Q, Wu Q, Halcomb RL, Saito RD, Schroeder SD, Lazerwith SE, Bondy S, Jin D, Hung M, Novikov N, Liu X, Villaseñor AG, Cannizzaro CE, Hu EY, Anderson RL, Appleby TC, Lu B, Mwangi J, Liclican A, Niedziela-Majka A, Papalia GA, Wong MH, Leavitt SA, Xu Y, Koditek D, Stepan GJ, Yu H, Pagratis N, Clancy S, Ahmadyar S, Cai TZ, Sellers S, Wolckenhauer SA, Ling J, Callebaut C, Margot N, Ram RR, Liu YP, Hyland R, Sinclair GI, Ruane PJ, Crofoot GE, McDonald CK, Brainard DM, Lad L, Swaminathan S, Sundquist WI, Sakowicz R, Chester AE, Lee WE, Daar ES, Yant SR, Cihlar T. [Clinical targeting of HIV capsid protein with a long-acting small molecule](#). *Nature*. 2020 Aug;584(7822):614-618. doi: 10.1038/s41586-020-2443-1. Epub 2020 Jul 1. PMID: 32612233; PMCID: PMC8188729.

9 Dvory-Sobol H, Shaik N, Callebaut C, Rhee MS. [Lenacapavir: a first-in-class HIV-1 capsid inhibitor](#). *Curr Opin HIV AIDS*. 2022 Jan 1;17(1):15-21. doi: 10.1097/COH.0000000000000713. PMID: 34871187.

10 SUNLENCA® (lenacapavir) [FDA label](#)

11 [NCT04150068](#)

12 CROI 2023 Feb 20-23 (ABSTRACT 193) Joseph J. Eron [Lenacapavir with bNABs GS-5423 and GS-2872 dosed every 6 months in people with hiv](#)

13 [NCT04143594](#)

14 Gupta SK, Berhe M, Crofoot G, Benson P, Ramgopal M, Sims J, McDonald C, Ruane P, Sanchez WE, Scribner A, Liu SY, VanderVeen LA, Dvory-Sobol H, Rhee MS, Baeten JM, Koenig E. [Lenacapavir administered every 26 weeks or daily in combination with oral daily antiretroviral therapy for initial treatment of HIV: a randomised, open-label, active-controlled, phase 2 trial](#). *Lancet HIV*. 2023 Jan;10(1):e15-e23. doi: 10.1016/S2352-3018(22)00291-0. PMID: 36566079.

15 Alex Durand Nka, Yagai Bouba, Georges Teto, Ezéchiel Ngoufack Jagni Semengue, Désiré Komego Takou, Aurelie Minelle Kengni Nguoko, Lavinia Fabeni, Luca Carioti, Daniele Armenia, Willy Pabo, Béatrice Dambaya, Samuel Martin Sosso, Vittorio Colizzi, Carlo-Federico Perno, Francesca Ceccherini-Silberstein, Maria Mercedes Santoro, Joseph Fokam, Alexis Ndjolo, [Evaluation of HIV-1 capsid genetic variability and lenacapavir \(GS-6207\) drug resistance-associated mutations according to viral clades among drug-naïve individuals](#). *Journal of Antimicrobial Chemotherapy*, Volume 78, Issue 1, January 2023, Pages 272–275, <https://doi.org/10.1093/jac/dkac388>

16 [NCT04925752](#) and [NCT04994509](#)

limit its co-administration of other drugs and it is currently advised not to co-administer lenacapavir with potent CYP/P-gp/UGT inducers (like rifampicin) ¹⁷.

Access

While lenacapavir is currently approved by the US FDA and EMA for heavily treatment-experienced adults, it is not yet registered (and is therefore not available) in any LMICs. While in the past Gilead has issued voluntary licences for all its previous HIV treatments, often before the product had reached regulatory approval (e.g. elvitegravir, cobicistat, TAF), access plans for lenacapavir in LMICs are not yet known.

Patent Status in LMICs

Several patents on lenacapavir have been filed or granted in LMICs expiring between 2034 and 2037 ¹⁸.

6.1.2 Ultra-long-acting injectable formulation for ARVs (University of North Carolina at Chapel Hill)

This candidate platform technology offers the ability to integrate multiple drugs into a single formulation that upon injection, releases the medicines over several weeks or months through an in-situ forming implant^{19,20}. It has potential applications for HIV treatment and/or prevention as well other indications including contraception, in the form of a multipurpose technology (MPT) ²¹⁻²². Its formulation with cabotegravir has shown protective effect in non-human primates' model ²³.

Access

Access plans for this long-acting technology and its applications are not yet known as it is in pre-clinical development.

Patent Status in LMICs

The international patent application covering this technology has recently been published and patents stemming from it will be expected to expire on 30.06.2042²⁴. The University of North Carolina, the applicant, has until the end of the year to decide in which countries to proceed with it (i.e. enter the national phase).

6.1.3 Islatravir (Merck Sharp and Dohme) for HIV treatment

Islatravir is a potent nucleoside reverse transcriptase translocation inhibitor (NRTTI), a new class of ARVs, with long-acting properties. In combination with doravirine, islatravir has been shown to be non-inferior to other ARV

17 Cilento ME, Ong YT, Tedbury PR, Sarafianos SG. [Drug Interactions in Lenacapavir-Based Long-Acting Antiviral Combinations](#). *Viruses*. 2022 May 31;14(6):1202. doi: 10.3390/v14061202. PMID: 35746673; PMCID: PMC9229705.

18 <https://www.medspace.org/?product%5B%5D=Lenacapavir&page=1>

19 Benhabbour SR, Kovarova M, Jones C, Copeland DJ, Shrivastava R, Swanson MD, Sykes C, Ho PT, Cottrell ML, Sridharan A, Fix SM, Thayer O, Long JM, Hazu da DJ, Dayton PA, Mumper RJ, Kashuba ADM, Victor Garcia J. [Ultra-long-acting tunable biodegradable and removable controlled release implants for drug delivery](#). *Nat Commun*. 2019 Sep 20;10(1):4324. doi: 10.1038/s41467-019-12141-5. PMID: 31541085; PMCID: PMC6754500.

20 Kovarova M, Benhabbour SR, Massud I, Spagnuolo RA, Skinner B, Baker CE, Sykes C, Mollan KR, Kashuba ADM, Garcia-Lerma JG, Mumper RJ, Garcia JV. [Ultra-long-acting removable drug delivery system for HIV treatment and prevention](#). *Nat Commun*. 2018 Oct 8;9(1):

21 Young IC, Benhabbour SR. [Multipurpose Prevention Technologies: Oral, Parenteral, and Vaginal Dosage Forms for Prevention of HIV/STIs and Unplanned Pregnancy](#). *Polymers (Basel)*. 2021 Jul 26;13(15):2450. doi: 10.3390/polym13152450. PMID: 34372059; PMCID: PMC

22 Friedland BA, Plagianos M, Savel C, Kallianes V, Martinez C, Begg L, Guthrie KM, Venkatesetty D, Pickett J, Haddad LB. [Women Want Choices: Opinions from the Share.Learn.Shape Global Internet Survey About Multipurpose Prevention Technology \(MPT\) Products in Development](#). *AIDS Behav*. 2023 Mar 7. doi: 10.1007/s10461-022-03951-8. Epub ahead of print. PMID: 36881183.

23 Young IC, Massud I, Cottrell ML, Shrivastava R, Maturavongsadit P, Prasher A, Wong-Sam A, Dinh C, Edwards T, Mrotz V, Mitchell J, Seixas JN, Pallerla A, Thorson A, Schauer A, Sykes C, De la Cruz G, Montgomery SA, Kashuba ADM, Heneine W, Dobard CW, Kovarova M, Garcia JV, Garcia-Lerma JG, Benhabbour SR. [Ultra-long-acting in-situ forming implants with cabotegravir protect female macaques against rectal SHIV infection](#). *Nat Commun*. 2023 Feb 9;14(1):708. doi: 10.1038/s41467-023-36330-5. PMID: 36759645; PMCID: PMC9911691.

24 https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2023278695&_cid=P11-LFR5LM-63396-1

regimens in a switch study²⁵. Several other studies were ongoing including applications for treatment, PrEP, PEP and long-acting subdermal implants, which highlight the high potential of the islatravir developing program.

However, in late 2021, Merck announced the clinical holds on all studies evaluating islatravir after reporting a decrease in total lymphocyte and CD4+ T-cell counts in some participants receiving islatravir in clinical studies, due to lymphocyte toxicity²⁶. More recently, the islatravir program has resumed but limiting the scope to HIV treatment only and using a low dose of islatravir, which is predicted to be safe (0.25mg QD and 2mg QW)²⁷. One new phase III study will evaluate once-daily islatravir plus doravirine in previously untreated people with HIV, and two trials will test the same combination as a switch option for people virologically suppressed on antiretroviral therapy²⁸. Additionally, the phase II trial of once-weekly oral islatravir plus lenacapavir will resume²⁹.

Access

Since development of this product has only recently resumed, plans for future access to this product in LMICs are not yet known.

Patent Status in LMICs

Patents on islatravir compound and its use for treating HIV- owned by Yamasa corporation and licensed exclusively to MSD – were mainly filed in HICs and Mexico and are expected to expire on 24.03.2025 (when calculating 20 years from the filing date).

A Patent family covering the use of Islatravir for the treatment or prophylaxis of HIV (dosing regimen less frequent than once-daily) owned by MSD includes patent applications filed in several LMICs countries/regions with an expected expiry in February 2037. Patents have been granted in South Africa, Georgia, Tunisia, Ukraine and patent applications are for example pending in ARIPO (African Regional Intellectual Property Organization), EAPO (Eurasian Patent Organization), Brazil, China, Dominican Republic, El Salvador, Iran and Malaysia.³⁰

6.2 Detailed assessment of HIV watchlist products

In this chapter, we provide additional information on the HIV medicines that are being listed in the watchlist.

6.2.1 Cabotegravir (ViiV Healthcare) for treatment

Cabotegravir is a small molecule belonging to the HIV-1 integrase strand transfer inhibitor (INSTI)³¹. Cabotegravir extended-release injectable suspension (VOCABRIA) and rilpivirine extended-release injectable suspension (REKAMBYS) are co-packaged under the name CABENUVA for intramuscular use for the treatment of HIV in virally suppressed adults as a 2-month intramuscular injectable³². However, the cold chain requirement of rilpivirine might limit its adoption in resource-limited settings. Recently, the SOLAR trial showed that switch to

²⁵ [SWITCH TO DOR/ISL \(100/0.75MG\) QD: WEEK 48 RESULTS FROM AN OPEN-LABEL PHASE 3 TRIAL - CROI 2023](#)

²⁶ [Press release: Merck Announces Clinical Holds on Studies Evaluating Islatravir for the Treatment and Prevention of HIV-1 Infection](#)

²⁷ Ryan C Vargo¹, Seth Robey¹, Xiaowei Zang¹, Lihong Du¹, Bhargava Kandala¹, Jessica Roberts², Stephanie Klopfer¹, Kathleen Squires¹ 1Merck & Co., Inc., Rahway NJ, USA; 2Simulation Plus, Cognigen Division, Buffalo, New York, USA. [MODELING TO OPTIMIZE ISLATRAVIR QW DOSE IN HIV VIROLOGICALLY SUPPRESSED PWH](#). CROI 2023

²⁸ [Press release: Merck Opens Enrollment in New Phase 3 Clinical Trials with Investigational Once-Daily Islatravir in Combination with Doravirine for Treatment of HIV-1 Infection](#)

²⁹ [NCT05052996](#)

³⁰ <https://www.medspal.org/?product%5B%5D=Islatravir&page=1>

³¹ Cattaneo D, Gervasoni C. [Pharmacokinetics and Pharmacodynamics of Cabotegravir, a Long-Acting HIV Integrase Strand Transfer Inhibitor](#). Eur J Drug Metab Pharmacokinet. 2019 Jun;44(3):319-327. doi: 10.1007/s13318-018-0526-2. PMID: 30387005.

³² [Cabenuva FDA Label](#)

CAB-RPV LA (2 months dosing) vs. staying on daily oral BIC/FTC/TAF in adults living with HIV had similar viral efficacy, and preferred by most patient with improved patient ART satisfaction ³³.

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%). The pharmacokinetic tail of cabotegravir injections, however, raises some worries about the potential emergence of drug resistance, even if this is more concerning in PrEP use. Cabotegravir co-administration with antimycobacterials (rifabutin, rifampin, rifapentine) may represent a challenge but it is compatible with most used contraceptive options in LMICs ³⁴. Cabotegravir is also being studied during pregnancy³⁵ but more data is needed on the long-acting cabotegravir and rilpivirine combination. Modelling studies suggests a decrease in plasma concentrations of CAB-RPV LA (4-week dosing) in pregnancies in early 2nd trimester, attributed to the predicted induction of UGT1A1 and CYP3A4 during the 2nd and 3rd trimesters, underscoring the need for PK studies in pregnancy.

Cabotegravir is also approved as an injection every 2 months for HIV PrEP ³⁶. MPP has secured the cabotegravir licence for PrEP from ViiV, in 2023.

Access

Cabotegravir long-acting (together with rilpivirine) for treatment has not yet been registered in LMICs and is therefore currently not available. Access plans in LMICs (if any) are not yet known. To date, WHO has not prioritized the treatment indication for CAB-LA and the licence between MPP and ViiV only covers the prevention indication. However, the formulation that is used for treatment is identical to the one used for prevention, and if CAB-LA were to be prioritized for treatment, consideration could be given to the inclusion of such indication in the licence.

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. MPP holds a licence with ViiV Healthcare for the use of Cabotegravir for PrEP³⁷.

6.2.2 GSK3640254 (ViiV Healthcare) for HIV treatment

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 ³⁸. Because of the new mechanism of action, GSK3640254 should have low cross-resistance with other approved ARV classes. GSK3640254 can be administered orally and without food restrictions ³⁹.

33 Moti N. Ramgopal, Antonella Castagna, Charles Cazanave, Vicens Diaz-Brito, Robin Dretler, Shinichi Oka, Olayemi Osiyemi, Kenneth Sutton, Denise Sutherland-Phillips, Alessandro Berni, Christine Latham8, Feifan Zhang, Ronald Dâ Amico, Kimberly Smith, Jean van Wyk. [SOLAR \(Switch Onto Long-Acting Regimen\) 12-Month Results -Randomized Switch Trial of CAB + RPV LA vs. Oral BIC/FTC/TAF](#). CROI 2023

34 [NCT02159131](#)

35 [NCT04518228](#)

36 [Apretude FDA label](#)

37 <https://medicinespatentpool.org/licence-post/cabotegravir-long-acting-la-for-hiv-pre-exposure-prophylaxis-prep>

38 Dicker I, Jeffrey JL, Protack T, Lin Z, Cockett M, Chen Y, Sit SY, Gartland M, Meanwell NA, Regueiro-Ren A, Drexler D, Cantone J, McAuliffe B, Krystal M. [GSK3640254 Is a Novel HIV-1 Maturation Inhibitor with an Optimized Virology Profile](#). *Antimicrob Agents Chemother*. 2022 Jan 18;66(1):e0187621. doi: 10.1128/AAC.01876-21. Epub 2021 Nov 15. PMID: 34780263; PMCID: PMC8765437.

39 [NCT04263142](#)

GSK3640254 is currently in phase IIb clinical trials after demonstrating a dose-related reduction in HIV-1 viral load over 7–10 days of dosing to HIV-1-infected subjects⁴⁰. The study provides limited but promising evidence of efficacy. It will be important to monitor the future developments of GSK3640254 and the efficacy data generated.

GSK3640254 safety data is limited but encouraging. It can be co-administered with DTG, TAF/FTC and oral contraceptives (ethinyl oestradiol and levonorgestrel). However, because of the new mechanism of action, more data will be needed on the developed phenotypic resistance in patients and their clinical implications.

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 2035⁴¹.

6.2.3 Doravirine (Merck Sharp and Dohme) for HIV treatment

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 transcriptase⁴².

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 history⁴³. 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 therapy⁴⁴. DRIVE-AHEAD was a phase III study comparing doravirine/lamivudine/tenofovir disoproxil fumarate to efavirenz/emtricitabine/tenofovir disoproxil fumarate⁴⁵. Both DRIVE studies were designed as non-inferiority trials and demonstrated doravirine to be non-inferior to the comparators used.

Importantly, doravirine is developed with islatravir. One new phase III study will now evaluate once-daily islatravir plus doravirine for previously untreated people with HIV, and two trials will test the combination as a switch option for people virologically suppressed on antiretroviral therapy⁴⁶.

Doravirine is also interesting for its potential as treatment for infants and it is studied in HIV infected children starting from 4 weeks of age up to 12 years and weighting less than 45kg⁴⁷. Additionally, a granular oral formulation has been developed⁴⁸.

40 Regueiro-Ren A, Sit SY, Chen Y, Chen J, Swidorski JJ, Liu Z, Venables BL, Sin N, Hartz RA, Protack T, Lin Z, Zhang S, Li Z, Wu DR, Li P, Kempson J, Hou X, Gupta A, Rampulla R, Mathur A, Park H, Sarjeant A, Benitex Y, Rahematpura S, Parker D, Phillips T, Haskell R, Jenkins S, Santone KS, Cockett M, Hanumegowda U, Dicker I, Meanwell NA, Krystal M. [The Discovery of GSK3640254, a Next-Generation Inhibitor of HIV-1 Maturation](#). *J Med Chem*. 2022 Sep 22;65(18):11927-11948. doi: 10.1021/acs.jmedchem.2c00879. Epub 2022 Aug 31. PMID: 36044257.

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

42 Talwani R, Temesgen Z. [Doravirine: a new non-nucleoside reverse transcriptase inhibitor for the treatment of HIV infection](#). *Drugs Today (Barc)*. 2020 Feb;56(2):113-124. doi: 10.1358/dot.2020.56.2.3109966. PMID: 32163527.

43 [Pifeltro FDA label](#)

44 Molina JM, Squires K, Sax PE, Cahn P, Lombaard J, DeJesus E, Lai MT, Rodgers A, Lupinacci L, Kumar S, Sklar P, Hanna GJ, Hwang C, Martin EA; [DRIVE-FORWARD trial group. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naïve adults with HIV-1 \(DRIVE-FORWARD\): 96-week results of a randomised, double-blind, non-inferiority, phase 3 trial](#). *Lancet HIV*. 2020 Jan;7(1):e16-e26. doi: 10.1016/S2352-3018(19)30336-4. Epub 2019 Nov 15. PMID: 31740348.

45 Orkin C, Squires KE, Molina JM, Sax PE, Sussmann O, Lin G, Kumar S, Hanna GJ, Hwang C, Martin E, Tepler H. [Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate \(TDF\) Versus Efavirenz/Emtricitabine/TDF in Treatment-naïve Adults With Human Immunodeficiency Virus Type 1 Infection: Week 96 Results of the Randomized, Double-blind, Phase 3 DRIVE-AHEAD Noninferiority Trial](#). *Clin Infect Dis*. 2021 Jul 1;73(1):33-42. doi: 10.1093/cid/ciaa822. PMID: 33336698; PMCID: PMC8246893.

46 [Press release: Merck Opens Enrollment in New Phase 3 Clinical Trials with Investigational Once-Daily Islatravir in Combination with Doravirine for Treatment of HIV-1 Infection](#)

47 [NCT04375800](#)

48 Yee, K.L., DiBenedetto, A., Fan, L. et al. [Comparative Bioavailability of Oral Granule Formulations of the HIV Antiretroviral Drugs Doravirine, Lamivudine, and Tenofovir Disoproxil Fumarate](#). *AAPS PharmSciTech* 21, 91 (2020). <https://doi.org/10.1208/s12249-020-1630-6>

Doravirine has an acceptable safety profile. Most common adverse reactions in trials were nausea, dizziness, headache, fatigue, diarrhoea, abdominal pain, and abnormal dreams. Doravirine is contraindicated with rifampicin and rifapentine, 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. Doravirine is also being studied as a possible alternative for people experiencing excessive weight gain on integrase inhibitors however, but no results are available yet ⁵⁰.

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 undisclosed manufacturers are known to have been granted covering 86 countries (all low-income countries, lower-middle-income countries, countries in Sub-Saharan Africa and least-developed countries) and generic versions of the product (including its combination with TDF/3TC) are likely in development⁵¹. Whether further licensing by MPP could contribute to improving access depends on the details of those licences, the likely future importance of the drug and the number of manufacturers that have received the licence.

Patent Status in LMICs

Patents on the doravirine compound and its combinations with other anti-HIV agents or antivirals have been filed in many LMICs and are expected to expire in 2031⁵². In few countries, the patent term may be extended by another five years, until 2036.

6.2.4 Rilpivirine (Janssen) for HIV treatment

Rilpivirine is a small molecule belonging to the NNRTI class ⁵³. Rilpivirine is approved as long-acting intramuscular injectable in combination with cabotegravir for the treatment of virally suppressed HIV patients (Cabenuva), which can be initiated with or without an oral lead-in period ⁵⁴. The long-acting properties of this formulation are favourable, however, the cold chain requirement of rilpivirine injections makes it less suitable for use in resource-limited settings. 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 ⁵⁵. Rilpivirine is also being studied in HIV-infected children and adolescents as oral and long-acting injectable with cabotegravir (MOCHA study) ⁵⁶.

Rilpivirine is considered safe, even if, a few considerations should be taken into account when using rilpivirine⁵⁷. 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

49 Lam E, Schaefer J, Zheng R, Zhan T, Kraft WK. [Twice-Daily Doravirine Overcomes the Interaction Effect from Once-Weekly Rifapentine and Isoniazid in Healthy Volunteers](#). Clin Transl Sci. 2020 Nov;13(6):1244-1250. doi: 10.1111/cts.12810. Epub 2020 May 29. PMID: 32407548; PMCID: PMC7719366.

50 [NCT04636437](#)

51 <https://www.merck.com/news/merck-enters-into-voluntary-licensing-agreements-for-doravirine-to-expand-patient-access-in-resource-limited-settings/>

52 <https://www.medsal.org/?product%5B%5D=Doravirine+100+mg&product%5B%5D=Doravirine%2FLamivudine%2FTenofovir+100%2F300%2F300+mg&page=1>

53 Fernández-Montero JV, Vispo E, Anta L, de Mendoza C, Soriano V. [Rilpivirine: a next-generation non-nucleoside analogue for the treatment of HIV infection](#). Expert Opin Pharmacother. 2012 May;13(7):1007-14. doi: 10.1517/14656566.2012.667802. PMID: 22519768.

54 [Cabenuva FDA Label](#)

55 Overton ET, Richmond G, Rizzardini G, Thalme A, Girard PM, Wong A, Porteiro N, Swindells S, Reynes J, Noe S, Harrington C, Español CM, Acupil C, Aksar A, Wang Y, Ford SL, Crauwels H, van Eygen V, Van Solingen-Ristea R, Latham CL, Thiagarajah S, D'Amico R, Smith KY, Vandermeulen K, Spreen WR. [Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection: 152-week results from ATLAS-2M, a randomized, open-label, Phase 3b, noninferiority study](#). Clin Infect Dis. 2023 Jan 20:ciad020. doi: 10.1093/cid/ciad020. Epub ahead of print. PMID: 36660819.

56 [NCT03497676](#)

57 [Cabenuva FDA Label](#)

(incidence > 2%) of at least moderate to severe intensity (> Grade 2) were depression, insomnia, headache and rash. A few NNRTI mutations have been associated with decreased susceptibility to rilpivirine, therefore, resistance to rilpivirine largely excludes future use of the NNRTI class. Additionally, rilpivirine plasma concentrations may change with co-administration with drugs that induce or inhibit CYP3A4, including rifampicin.

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 injectable formulation of rilpivirine are not known.

Patent Status in LMICs

Patents on rilpivirine compound expired in 2022, except for six countries where the term has been extended until 2026-2027. There are patents on the aqueous suspensions of rilpivirine micro- or nanoparticles (relevant to the long-acting formulation) as well as patents on the intermittent administration of rilpivirine parenteral formulation (in the range of one week to one year) 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 alafenamide⁵⁸.

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.

6.2.5 Three monthly dual vaginal ring for HIV PrEP and prevention of unintended pregnancy (Population Council)

This intravaginal ring made of a flexible polymer is a female-initiated drug delivery device intended for use over a period of 90 days as a tool to prevent HIV acquisition and unintended pregnancy. It combines dapivirine, a microbicide, and levonorgestrel, a progestin used for contraception^{59,60}. While this product is still in early development (two phase I completed)⁶¹, the monthly dapivirine ring current roll-out is helping pave the way to the introduction of next generation rings if proven safe and effective^{62,63,64}.

Access

Access plans for the three-monthly vaginal multipurpose ring are not yet known.

Patent Status in LMICs

The International Partnership for Microbicides (IPM) has patent applications covering platinum-catalysed intravaginal drug delivery device pending in Canada and with the European Patent Office (EPO). If granted, the European patent could be validated in the following LMICs: Albania, Bulgaria, North Macedonia, Serbia, Turkey,

58 <https://www.medspal.org/?keywords=rilpivirine&page=4>

59 <https://theimpt.org/mpts-technology-landscape-and-potential-for-low-and-middle-income-countries/>

60 Murphy DJ, Dallal Bashi YH, McCoy CF, Boyd P, Brown L, Martin F, McMullen N, Kleinbeck K, Dangi B, Spence P, Hansraj B, Devlin B, Malcolm RK. *In vitro drug release, mechanical performance and stability testing of a custom silicone elastomer vaginal ring releasing dapivirine and levonorgestrel*. Int J Pharm X. 2022 Jan 25;4:100112. doi: 10.1016/j.ijpx.2022.100112. PMID: 35128382; PMCID: PMC8804184.

61 S. Achilles, C.W. Kelly, D.L. Blithe, J. Long, B.A. Richardson, B. Devlin, C.W. Hendrix, S.M. Poloyac, M.A. Marzinke, D. Singh, J.M. Piper, J. Steytler, B.A. Chen. *Pharmacokinetics, safety, and vaginal bleeding associated with continuous versus cyclic 90-day use of dapivirine and levonorgestrel vaginal rings for multipurpose prevention of HIV and pregnancy*. HIVR4PVirtual

62 Ridgeway K, Montgomery ET, Smith K, Torjesen K, van der Straten A, Achilles SL, Griffin JB. Vaginal ring acceptability: *A systematic review and meta-analysis of vaginal ring experiences from around the world*. Contraception. 2022 Feb;106:16-33. doi: 10.1016/j.contraception.2021.10.001. Epub 2021 Oct 10. PMID: 34644609; PMCID: PMC9128798.

63 Mirembe BG, Cabrera MV, van der Straten A, Nakalega R, Cobbing M, Mgodini NM, Palanee-Phillips T, Mayo AJ, Dadabhai S, Mansoor LE, Siva S, Nair G, Chinula L, Akello CA, Nakabiito C, Soto-Torres LE, Baeten JM, Brown ER. *Correlates of Dapivirine Vaginal Ring Acceptance among Women Participating in an Open Label Extension Trial*. AIDS Behav. 2023 Mar;27(3):1030-1043. doi: 10.1007/s10461-022-03841-z. Epub 2022 Sep 6. PMID: 36066762.

64 Griffin JB, Ridgeway K, Montgomery E, Torjesen K, Clark R, Peterson J, Baggaley R, van der Straten A. *Vaginal ring acceptability and related preferences among women in low- and middle-income countries: A systematic review and narrative synthesis*. PLoS One. 2019 Nov 8;14(11):e0224898. doi: 10.1371/journal.pone.0224898. PMID: 31703094; PMCID: PMC6839883.

Montenegro and Morocco. The expected expiry is 22.10.2035 and the equivalent international patent published as WO2016065096.

6.3 Detailed assessments of TB priorities

In this chapter we provide additional information on the TB medicines that are listed in the priority list.

6.3.1 Bedaquiline (Janssen)

Bedaquiline is an 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 TB⁶⁵. As per WHO guidelines⁶⁶, 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. 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 Indian generic manufacturers are likely to enter the market at that time (particularly following the recent rejection of the fumarate salt patent in India), 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.

6.3.2 Quabodepistat (Otsuka)

Quabodepistat (OPC-167832) is an Otsuka investigational phase II drug being studied for TB treatment⁶⁷. Quabodepistat is a carbostyryl 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 μ g/mL) against both growing and intracellular bacilli.

This compound is being developed in a phase I/II trial of multiple oral doses of quabodepistat for uncomplicated pulmonary tuberculosis by Otsuka, in collaboration with the Bill and Melinda Gates Foundation⁶⁸. A recent publication from Otsuka has suggested that quabodepistat in regimens combined with delamanid showed superior efficacy to a standard regimen RHZE (rifampicin, isoniazid, pyrazinamide and ethambutol) in mice⁶⁹. Importantly, it is now studied as part of a new, promising, TB regimen under the Project to Accelerate New

⁶⁵ [NCT03338621](https://clinicaltrials.gov/ct2/show/study/NCT03338621)

⁶⁶ https://www.who.int/tb/publications/2019/rapid_communications_MDR/en/

⁶⁷ <https://www.otsuka-us.com/research>

⁶⁸ [NCT03678688](https://clinicaltrials.gov/ct2/show/study/NCT03678688)

⁶⁹ <https://aac.asm.org/content/aac/early/2020/03/25/AAC.02020-19.full.pdf>

Treatments for Tuberculosis (PAN-TB) program, in combination with delamanid, bedaquiline, and sutezolid (DBOS) or in combination with pretomanid, bedaquiline and sutezolid (PBOS)⁷⁰.

Access

Access plans for quabodepistat in LMICs are unknown. For its previous TB molecule, delamanid, Otsuka had provided an exclusive licence to one manufacturer. Broader non-exclusive licensing through MPP could contribute to improved affordability for a molecule that may become part of a pan-TB regimen.

Patent Status in LMICs

The compound patent on quabodepistat has been filed or granted in several LMICs and is expected to expire in 2035⁷¹.

6.4 Detailed assessments of TB watchlist products

In this chapter we provide additional information on the TB medicines that are listed in the watchlist.

6.4.1 BTZ-043 (University of Munich and the German Center for Infection Research)

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 indicated that BTZ-043 was safe and well tolerated up to 500 mg⁷². 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 2019⁷³, but the results for this study 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 2026⁷⁴. Secondary patents have not been identified.

6.4.2 Delpazolid (LegoChem BioSciences)

Delpazolid is an investigational phase II drug developed by LegoChem BioSciences Inc. 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 2020⁷⁵, 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 practice⁷⁶. A phase IIb dose-finding study has

⁷⁰ <https://www.tballiance.org/news/pan-tb-collaboration-advance-investigational-tuberculosis-drug-regimens-phase-2-clinical-trials>

⁷¹ [https://www.medspal.org/?product%5B%5D=Quabodepistat+\(OPC-167832\)&page=1](https://www.medspal.org/?product%5B%5D=Quabodepistat+(OPC-167832)&page=1)

⁷² [NCT0359060](https://www.clinicaltrials.gov/ct2/show/study/NCT0359060)

⁷³ [NCT04044001](https://www.clinicaltrials.gov/ct2/show/study/NCT04044001)

⁷⁴ <https://www.medspal.org/?product%5B%5D=BTZ-043&page=1>

⁷⁵ [NCT02836483](https://www.clinicaltrials.gov/ct2/show/study/NCT02836483)

⁷⁶ Kim JS, Kim YH, Lee SH, Kim YH, Kim JW, Kang JY, Kim SK, Kim SJ, Kang YS, Kim TH, Mok J, Byun MK, Park HJ, Joh JS, Park YB, Lim HS, Choi H, Lee SH, Kim H, Yang J, Kim H, Shen X, Al Sultan A, Cho I, Geiter L, Shim TS. [Early Bactericidal Activity of Delpazolid \(LCB01-0371\) in Patients with Pulmonary Tuberculosis](https://doi.org/10.1128/AAC.01684-21). *Antimicrob Agents Chemother*. 2022 Feb 15;66(2):e0168421. doi: 10.1128/AAC.01684-21. Epub 2021 Dec 6. PMID: 34871098; PMCID: PMC8846473.

started to study delpazolid, in combination with bedaquiline, delamanid and moxifloxacin, to treat adult patients with newly diagnosed, smear positive, uncomplicated, drug sensitive pulmonary tuberculosis (TB) ⁷⁷.

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 2029⁷⁸.

6.4.3 GSK3036656 (GlaxoSmithKline)

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 studies⁷⁹. Results from a phase IIa study showed that GSK3036656 was well tolerated and showed early bactericidal activity with a low, once-daily oral dose after 14 days of treatment in participants with drug-susceptible pulmonary tuberculosis ^{80,81}.

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 2031-2036⁸².

6.4.4 Macozinone (Swiss Federal Institute of Technology Lausanne)

Macozinone is an investigational drug developed by the non-profit Innovative Medicines for Tuberculosis (iM4TB) foundation ⁸³. 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. A dose-escalation phase I study in healthy male volunteers followed by a multiple ascending dose, showed promising safety profile of the drug ⁸⁴. The company Nearmedic Plus, which leads macozinone development for the Russian market and associated countries, terminated a phase IIa trial due to very slow enrolment ⁸⁵.

⁷⁷ [NCT04550832](https://www.clinicaltrials.gov/ct2/show/study/NCT04550832)

⁷⁸ <https://www.medspal.org/?product%5B%5D=Delpazolid&page=1>

⁷⁹ [NCT03075410](https://www.clinicaltrials.gov/ct2/show/study/NCT03075410)

⁸⁰ [NCT03557281](https://www.clinicaltrials.gov/ct2/show/study/NCT03557281)

⁸¹ Press release: <https://www.gsk.com/en-gb/media/press-releases/gsk-announces-positive-phase-ii-study-results-for-a-new-first-in-class-candidate-medicine/>

⁸² <https://www.medspal.org/?product%5B%5D=GSK3036656&page=1>

⁸³ [iM4TB Foundation](https://www.im4tb.org/)

⁸⁴ [NCT03776500](https://www.clinicaltrials.gov/ct2/show/study/NCT03776500)

⁸⁵ [NCT03036163](https://www.clinicaltrials.gov/ct2/show/study/NCT03036163)

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 (Brazil, China, Georgia, Indonesia, India, Mongolia, South Africa, Ukraine, Uzbekistan, Eurasia (AM, BY, KG, KZ, RU, MD) and is expected to expire in 2031.

6.4.5 Telacebec (Qurient Co. Ltd)

Telacebec is an investigational phase II drug studied for TB treatment and it is a first-in-class selective inhibitor of the *Mycobacterium tuberculosis* cytochrome bc1 complex, which is a critical component of the bacteria energy metabolism⁸⁶. A phase IIa trial showed promising early bactericidal activity in March 2020⁸⁷. 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.

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 2031⁸⁸.

6.4.6 Fobrepodacin (Spero Therapeutics, LLC, Bill & Melinda Gates Medical Research Institute)

Fobrepodacin (SPR720) is an orally administered investigational antibacterial agent that targets enzymes essential for bacterial DNA replication⁸⁹. SPR720 was developed for the treatment of infections caused by non-tuberculous mycobacteria but it showed potential to treat drug-susceptible TB and for XDR TB infections.

Access

While there are no specific access plans announced, Fobrepodacin is co-developed together with the Bill & Melinda Gates Medical Research Institute, a public health organization with global access plans.

86 de Jager VR, Dawson R, van Niekerk C, Hutchings J, Kim J, Vanker N, van der Merwe L, Choi J, Nam K, Diacon AH. [Telacebec \(Q203\), a New Antituberculosis Agent](#). *N Engl J Med*. 2020 Mar 26;382(13):1280-1281. doi: 10.1056/NEJMc1913327. PMID: 32212527.

87 [NCT03563599](#)

88 <https://www.medspal.org/?page=1>

89 <https://www.newtdrugs.org/pipeline/compound/spr720-fobrepodacin>

Patent Status in LMICs

The compound patent on fobrepodacin has been granted in a limited number of LMICs including India and is expected to expire in 2032. Secondary patents identified belonging to Vertex covering e.g. manufacturing processes, solid forms or combinations have only been filed in few HICs.

6.4.7 Sudapyridine (Shanghai Jiata Biotech)

A novel diarylpyridine series was recently developed using bedaquiline chemical structure as reference⁹⁰. From this development program, sudapyridine was identified as a promising anti-mycobacterial agent against *M. tuberculosis* H37Rv in vitro and in vivo and low cytotoxicity; sudapyridine has promising pharmacokinetic parameters in animals, better lung exposure and lower QTc prolongation potential compared to bedaquiline. It is currently under clinical phase II development⁹¹.

Access

Access plans for sudapyridine in LMICs are unknown.

Patent Status in LMICs

The compound patent on sudapyridine has been granted in a limited number of LMICs including India and is expected to expire in 2035. The only secondary patent identified so-far belonging to Shanghai Jiata Biotech (co-ownership with Cisen Pharmaceutical Co., Ltd) and covering manufacturing processes and intermediates was filed and granted only in China and Taiwan.

6.5 Detailed assessment of viral hepatitis watchlist product

In this chapter we provide additional information on the viral hepatitis medicines that are being listed in the priority list.

6.5.1 Bulevirtide (Gilead)

Bulevirtide, a viral entry inhibitor, is an antiviral medicine effective in decreasing HDV replication. It is conditionally approved for chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult patients with compensated liver disease⁹².

Bulevirtide is administered as a daily injection (2mg) by subcutaneous injection as monotherapy or in co-administration with a nucleoside/nucleotide analogue for treatment of underlying HBV. Data are available from several clinical trials, as well as real-world studies from Europe, where the drug is available through conditional approval. Virologic response rates from real-world studies have been similar to those from clinical trials (more than 50% at Week 24)⁹³. Now we have efficacy data of bulevirtide administered up to 72 weeks from HEP4Di, a retrospective, real-world analysis of 93 patients with HDV from Italy. Virologic response was achieved by 75% of patients at Week 72 of treatment. However, the optimal treatment duration is unknown and while it is very

90 Yao R, Wang B, Fu L, Li L, You K, Li YG, Lu Y. [Sudapyridine \(WX-081\), a Novel Compound against Mycobacterium tuberculosis](#). *Microbiol Spectr*. 2022 Feb 23;10(1):e0247721. doi: 10.1128/spectrum.02477-21. Epub 2022 Feb 16. PMID: 35170994; PMCID: PMC8849072.

91 [NCT04608955](#)

92 [Hepcludex - EMA Label](#)

93 Lampertico P, Roulot D, Wedemeyer H. [Bulevirtide with or without pegIFNα for patients with compensated chronic hepatitis delta: From clinical trials to real-world studies](#). *J Hepatol*. 2022 Nov;77(5):1422-1430. doi: 10.1016/j.jhep.2022.06.010. Epub 2022 Jun 22. PMID: 35752223.

promising that some patients have maintained a durable response, it is suggested that HDV might become active again after stopping bulevirtide.

Access

Access plans for bulevirtide in LMICs are unknown. For its oral hepatitis C medicines Gilead had issued voluntary licensing agreements to multiple manufacturers, but it is unclear whether a similar approach would be taken for this medicine.

Patent Status in LMICs

The compound patent on bulevirtide has been granted in a limited number of LMICs (including India, Russia, China, Brazil and South Africa) where it is expected to expire in 2028.

6.6 Detailed assessments of oncology priorities

6.6.1 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 cancer⁹⁴. The WHO EML Expert Committee acknowledged that osimertinib had meaningful overall survival benefit compared to the first- and second-generation of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR-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 EGFR-TKIs currently on the EML. Further, the Committee called on MPP to explore licensing opportunities for osimertinib and welcomed resubmission in future EML updates. It was resubmitted in 2023 to the EML⁹⁵.

Clinical Relevance

2.2 million incident cases of lung cancer were reported in 2020⁹⁶ and more than 80% are classified as non-small cell cancers (NSCLC). The EGFR mutation is present in 30% of these cases and almost 60% are diagnosed in advanced stages⁹⁷. The European Society for Medical Oncology (ESMO) considers EGFR-TKIs the standard of care for first line treatment for advanced EGFR-mutated NSCLC⁹⁸. First and second generations of EGFR-TKIs have shown an improvement in terms of objective response rate (ORR) and progression free survival (PFS) versus platinum-based chemotherapy¹¹⁵. 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)⁹⁹.

94 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

95 https://cdn.who.int/media/docs/default-source/essential-medicines/2023-eml-expert-committee/applications-for-addition-of-new-medicines/a30_osimertinib.pdf?sfvrsn=5c587764_2

96 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. *Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries*. *CA Cancer J Clin*. 2021 May;71(3):209-249. doi: 10.3322/caac.21660. Epub 2021 Feb 4. PMID: 33538338.

97 <https://www.who.int/publications/i/item/9789240041134>

98 Remon J, Soria JC, Peters S; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. *Early and locally advanced non-small-cell lung cancer: an update of the ESMO Clinical Practice Guidelines focusing on diagnosis, staging, systemic and local therapy*. *Ann Oncol*. 2021 Dec;32(12):1637-1642. doi: 10.1016/j.annonc.2021.08.1994. Epub 2021 Sep 1. PMID: 34481037.

99 <https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-123-1>

Access in LMICs

Osimertinib is generally not available or affordable in many LMICs. Access plans for osimertinib in LMICs are unknown. The originator, Astra Zeneca, joined the Access To Oncology Medicines, ATOM, coalition, since its launch, in May 2022. This global initiative, convened by the Union for International Cancer Control, with several civil societies, public, and private sector partners (including the Medicines Patent Pool), aims to provide coordinated efforts towards the provision of comprehensive cancer care in LMICs, including strengthening the supply chain, capacity building, advocacy, demand generation, and training.

Patent Status in LMICs

The primary patent on osimertinib is expected to expire in 2032 and has been granted in a large number of LMICs. The patent term has been extended in few countries until 2036 (Belarus) and 2033 (Kazakhstan). Secondary formulation patents are expiring in 2035, also filed with a wide geographical scope¹⁰⁰.

6.6.2 Aumolertinib (Hansoh Pharma/EQRx)

Indication

For treatment of epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC).

Clinical Relevance

A phase III double-blind trial evaluated the efficacy and safety of aumolertinib versus gefitinib (1st generation) as first-line treatment for locally advanced or metastatic EGFR-mutated non-small cell lung cancer (NSCLC). Aumolertinib has demonstrated a consistent PFS benefit and a lower rate of adverse events leading to permanent discontinuation¹⁰¹.

Access in LMICs

Aumolertinib is being developed in partnership with EQRx, a company “committed to the development and delivery of important new medicines at lower prices”, although the actual access plans for LMICs are unclear at present¹⁰².

Patent Status in LMICs

Aumolertinib compound patent is expected to expire in 2035 and it has been granted in many countries including India. Secondary patents covering polymorphic forms or formulations with expiry dates in 2036 and 2039 were filed mainly in HICs.

6.6.3 Ribociclib (Novartis); Abemaciclib (Eli Lilly)

Potential EML indication

Cyclin-dependent kinase (CDK) 4/6 inhibitors were submitted for inclusion in the EML for the treatment of Hormone Receptor (HR) positive Human Epidermal Growth Factor Receptor 2 (HER2) negative (or HR+/HER2-) advanced breast cancer¹⁰³. The Expert Committee acknowledged that CDK4/6 inhibitors had potential for future

100 <https://www.medspal.org/?product%5B%5D=Osimertinib+80+mg&page=1>

101 Lu S, Dong X, Jian H, Chen J, Chen G, Sun Y, Ji Y, Wang Z, Shi J, Lu J, Chen S, Lv D, Zhang G, Liu C, Li J, Yu X, Lin Z, Yu Z, Wang Z, Cui J, Xu X, Fang J, Feng J, Xu Z, Ma R, Hu J, Yang N, Zhou X, Wu X, Hu C, Zhang Z, Lu Y, Hu Y, Jiang L, Wang Q, Guo R, Zhou J, Li B, Hu C, Tong W, Zhang H, Ma L, Chen Y, Jie Z, Yao Y, Zhang L, Jie W, Li W, Xiong J, Ye X, Duan J, Yang H, Sun M, Sun C, Wei H, Li C, Ali SM, Miller VA, Wu Q. *AENEAS: A Randomized Phase III Trial of Aumolertinib Versus Gefitinib as First-Line Therapy for Locally Advanced or Metastatic Non-Small-Cell Lung Cancer With EGFR Exon 19 Deletion or L858R Mutations*. *J Clin Oncol*. 2022 Sep 20;40(27):3162-3171. doi: 10.1200/JCO.21.02641. Epub 2022 May 17. PMID: 35580297.

102 <https://www.eqr.com/us-en/press-release/aumolertinib-phase-iii-study-meets-primary-endpoint-in-first-line-treatment-for-patients-with-egfr-mutated-advanced-non-small-cell-lung-cancer/>

103 <https://apps.who.int/iris/bitstream/handle/10665/330668/9789241210300-eng.pdf?sequence=1&isAllowed=y>

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. CDK4/6 inhibitors were resubmitted in 2023 to the EML¹⁰⁴.

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^{105,106} or second line setting¹⁰⁷. The use of CDK4/6 inhibitors showed a significant improvement in survival and quality of life¹⁰⁸. 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 diarrhoea and fatigue, but lower rate of hematopoietic SE (including neutropenia)^{109,110}. A recent press release from the phase III NATALEE study announces that ribociclib significantly reduces the risk of disease recurrence compared to standard adjuvant endocrine therapy alone, with a consistent benefit in patients with earlier stages of breast cancer¹¹¹.

Access in LMICs

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 ribociclib¹¹². 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 leukaemia (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 in combination)¹¹³. Both the originators, Eli Lilly and Novartis, joined the Access To Oncology Medicines, ATOM, coalition, since its launch, in May 2022. This global initiative, convened by the Union for International Cancer Control, with several civil societies, public, and private sector partners (including the Medicines Patent Pool), aims to provide coordinated efforts towards the provision of comprehensive cancer care in LMICs, including strengthening the supply chain, capacity building, advocacy, demand generation, and training.

Patent Status in LMICs

104 <https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/24th-emi-expert-committee/a12-cyclin-dependent-kinase-4-6-inhibitors---hr-positive-her2-negative-advanced-breast-cancer---eml>

105 <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>

106 <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>

107 <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>

108 [https://jncn.org/configurable/content/journals\\$002fjncn\\$002f17\\$002f3.5\\$002farticle-pCLO19-059.xml?t:ac=journals%24002fjncn%24002f17%24002f3.5%24002farticle-pCLO19-059.xml](https://jncn.org/configurable/content/journals$002fjncn$002f17$002f3.5$002farticle-pCLO19-059.xml?t:ac=journals%24002fjncn%24002f17%24002f3.5%24002farticle-pCLO19-059.xml)

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

110 Thill M, Schmidt M. [Management of adverse events during cyclin-dependent kinase 4/6 \(CDK4/6\) inhibitor-based treatment in breast cancer](#). *Ther Adv Med Oncol*. 2018 Sep 3;10:1758835918793326. doi: 10.1177/1758835918793326. Erratum in: *Ther Adv Med Oncol*. 2018 Dec 03;10:1758835918810116. PMID: 30202447.

111 <https://www.novartis.com/news/media-releases/novartis-kisqali-phase-iii-natalee-trial-meets-primary-endpoint-interim-analysis-demonstrating-clinically-meaningful-benefit-broad-population-patients-early-breast-cancer>

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

113 <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/>

Patents on all three CDK 4/6 inhibitors have been filed in several LMICs. For ribociclib primary patents filed in many LMICs expire in 2027-2029 with secondary patents expiring in 2031-2036¹¹⁴; for abemaciclib primary patents expire in 2029 and filed in a high number of LMICs¹¹⁵.

6.6.4 Ibrutinib (AbbVie/Janssen); Zanubrutinib (Beighe)

EML indication

Ibrutinib has been included on the complementary list of the EML for the treatment of relapsed/refractory chronic lymphocytic leukaemia (CLL) (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 leukaemia compared with chemo-immunotherapy¹¹⁶. 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. It was resubmitted in 2023 to the EML¹¹⁷.

Clinical Relevance

CLL is the most common form of leukaemia in Western countries (30% of new cases). An estimated 100,000 cases were estimated to have occurred globally in 2019¹¹⁸. 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 cancers¹¹⁹.

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). In a recent head-to-head trial comparing ibrutinib to zanubrutinib in the treatment of relapsed or refractory CLL, progression-free survival was significantly longer among patients who received zanubrutinib¹²⁰.

Access in LMICs

Ibrutinib has been filed for registrations/registered in, among others, six high-burden LMICs¹²¹. There are limited details on access plans in LMICs.

114 <https://www.medspal.org/?keywords=ribociclib&page=1>

115 <https://www.medspal.org/?keywords=abemaciclib&page=1>

116 <https://www.who.int/publications/i/item/9789240041134>

117 https://cdn.who.int/media/docs/default-source/essential-medicines/2023-eml-expert-committee/applications-for-addition-of-new-medicines/a52_zanubrutinib.pdf?sfvrsn=574e2085_2

118 [https://biomedical-engineering-online.biomedcentral.com/articles/10.1186/s12938-021-00973-6#:~:text=Globally%2C%20during%20the%20last%2030,1.92%20\(Table%201\).](https://biomedical-engineering-online.biomedcentral.com/articles/10.1186/s12938-021-00973-6#:~:text=Globally%2C%20during%20the%20last%2030,1.92%20(Table%201).)

119 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

120 Brown JR, Eichhorst B, Hillmen P, Jurczak W, Kaźmierczak M, Lamanna N, O'Brien SM, Tam CS, Qiu L, Zhou K, Simkovic M, Mayer J, Gillespie-Twardy A, Ferrajoli A, Ganly PS, Weinkove R, Grosicki S, Mital A, Robak T, Osterborg A, Yimer HA, Salmi T, Wang MD, Fu L, Li J, Wu K, Cohen A, Shadman M. [Zanubrutinib or ibrutinib in Relapsed or Refractory Chronic Lymphocytic Leukemia](#). *N Engl J Med*. 2023 Jan 26;388(4):319-332. doi: 10.1056/NEJMoa2211582. Epub 2022 Dec 13. PMID: 36511784.

121 https://accessmedicinefoundation.org/media/uploads/downloads/613f5fb390319_Access_to_Medicine_Index_2021.pdf

Patent Status in LMIC

Ibrutinib compound patent expires in 2026 and it has been granted in few LMICs, including India. Many secondary patents with expiry dates ranging between 2031 and 2036 covering formulations, method or treatment or crystalline forms¹²².

The primary patent on zanubrutinib was granted in few LMICs where it is expected to expire in 2034. Secondary patents on crystalline forms are expected to expire in 2037¹²³.

6.6.5 Immune check-point inhibitors

EML indication

Two immune check-point inhibitors (ICI), 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).

Clinical relevance

Immune check-point inhibitor therapy has become part of the standard treatment of patients with advanced and metastatic NSCLC in many high-income settings, based on favourable improvements in clinical outcomes. Immune check-point 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 check-point inhibitors was mostly restricted to patients with PD-L1-positive tumours. Addition of immune check-point inhibitors to conventional chemotherapy was associated with a modest increase in toxicity, which may require highly specialised management in selected cases¹²⁴.

The Committee recognised the important role of immune check-point inhibitors as a therapeutic class in the treatment of NSCLC and would welcome a comprehensive review of all available immune check-point inhibitors used in the treatment of NSCLC, providing data on duration of therapy, for consideration by the Expert Committee in 2023¹²⁵. An application for the inclusion of pembrolizumab, atezolizumab, cemiplimab and durvalumab was resubmitted to the 2023 WHO Expert Committee on the Selection and Use of Essential Medicines¹²⁶.

Tislelizumab was submitted in 2021 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 check-point inhibitors used in the treatment of urothelial cancer for future consideration. An application was resubmitted to the 2023 WHO Expert Committee on the Selection and Use of Essential Medicines¹²⁷.

The Committee also considered that immune check-point 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.

122 <https://www.medspal.org/?keywords=ibrutinib&page=1>

123 <https://www.medspal.org/?keywords=zanubr&page=1>

124 Park Y-J, Kuen D-S, Chung Y. [Future prospects of immune check-point blockade in cancer: from response prediction to overcoming resistance](#). *Exp Mol Med*. 2018;50(8):109.

125 <https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2021.02>

126 https://cdn.who.int/media/docs/default-source/essential-medicines/2023-eml-expert-committee/applications-for-addition-of-new-medicines/a5_anti-pd-1_1_i.pdf?sfvrsn=194273c1_2

127 https://cdn.who.int/media/docs/default-source/essential-medicines/2023-eml-expert-committee/applications-for-addition-of-new-medicines/a46_tislelizumab.pdf?sfvrsn=2d9c10a2_2

In response to the WHO EML recommendation and considering 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 in LMICs

Access to ICIs is reported to be extremely low and challenging in LMICs¹²⁸. 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. However, several originators, e.g. Beigene joined the Access To Oncology Medicines, ATOM, coalition launched in May 2022. This global initiative, convened by the Union for International Cancer Control, with several civil societies, public, and private sector partners (including the Medicines Patent Pool), aims to provide coordinated efforts towards the provision of comprehensive cancer care in LMICs, including strengthening the supply chain, capacity building, advocacy, demand generation, and training.

Patent Status in LMICs

Pembrolizumab (Merck), atezolizumab (Genentech) 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.

6.7 Detailed assessments of oncology watchlist products

6.7.1 Furmonertinib (Allist); Lazertinib (Janssen)

Indication

For treatment of epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) (same drug class as osimertinib and aumolertinib).

Clinical performance

Furmonertinib showed superior efficacy compared with gefitinib as first-line therapy in Chinese patients with EGFR mutation-positive NSCLC, along with an acceptable safety profile without new signals. Furmonertinib is a new potential treatment option for this population¹²⁹.

Lazertinib is approved for treatment of EGFR mutant NSCLC in Korea. Lazertinib had manageable safety profile, durable antitumour efficacy, with clinically meaningful activity against brain metastases in patients with advanced or metastatic EGFR mutant NSCLC who had previously received EGFR TKIs¹³⁰.

Access in LMICs

The actual access plans for LMICs are not clear at present.

Patent status in LMICs

Primary patent expiry is 2035 for both furmonertinib and lazertinib.

128 Fundytus A, Sengar M, Lombe D, Hopman W, Jalink M, Gyawali B, Trapani D, Roitberg F, De Vries EGE, Moja L, Ilbawi A, Sullivan R, Booth CM. [Access to cancer medicines deemed essential by oncologists in 82 countries: an international, cross-sectional survey](#). *Lancet Oncol*. 2021 Oct;22(10):1367-1377. doi: 10.1016/S1470-2045(21)00463-0. Epub 2021 Sep 21. PMID: 34560006.

129 Shi Y, Chen G, Wang X, Liu Y, Wu L, Hao Y, Liu C, Zhu S, Zhang X, Li Y, Liu J, Cao L, Cheng Y, Zhao H, Zhang S, Zang A, Cui J, Feng J, Yang N, Liu F, Jiang Y, Gu C; FURLONG investigators. [Furmonertinib \(AST2818\) versus gefitinib as first-line therapy for Chinese patients with locally advanced or metastatic EGFR mutation-positive non-small-cell lung cancer \(FURLONG\): a multicentre, double-blind, randomised phase 3 study](#). *Lancet Respir Med*. 2022 Nov;10(11):1019-1028. doi: 10.1016/S2213-2600(22)00168-0. Epub 2022 Jun 2. PMID: 35662408.

130 Cho BC, Han JY, Kim SW, Lee KH, Cho EK, Lee YG, Kim DW, Kim JH, Lee GW, Lee JS, Shim BY, Kim JS, Chun SH, Lee SS, Kim HR, Hong MH, Ahn JS, Sun JM, Lee Y, Lee DH, Kang JA, Lee N, Kwon MJ, Espenschied C, Yablonovitch A, Ahn MJ. [A Phase 1/2 Study of Lazertinib 240 mg in Patients With Advanced EGFR T790M-Positive NSCLC After Previous EGFR Tyrosine Kinase Inhibitors](#). *J Thorac Oncol*. 2022 Apr;17(4):558-567. doi: 10.1016/j.jtho.2021.11.025. Epub 2021 Dec 24. Erratum in: *J Thorac Oncol*. 2022 Oct 22; PMID: 34958928.

6.7.2 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

In 2020, approximately 1.4 million men globally were diagnosed with prostate cancer¹³¹. Prostate cancer is the second most common cancer in men and is the most common cancer among men, with rising incidence rates, in sub-Saharan Africa^{132,133}. 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 cancer¹³⁴.

While prostate cancer generally has a favourable 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 in LMICs

Astellas' country teams provide several 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 included¹³⁵.

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 rationalisation¹³⁶.

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 Africa¹³⁷. 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

131 https://gco.iarc.fr/today/online-analysis-pie?v=2020&mode=cancer&mode_population=continents&population=900&populations=900&key=total&sex=0&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=7&group_cancer=1&include_nmcs=1&include_nmcs_other=1&half_pie=0&donut=0

132 <https://canceratlas.cancer.org/the-burden/sub-saharan-africa/>

133 Seraphin TP, Joko-Fru WY, Kamaté B, Chokunonga E, Wabinga H, Somdyala NIM, Manraj SS, Ogunbiyi OJ, Dzumalala CP, Finesse A, Korir A, N'Da G, Lorenzoni C, Liu B, Kantelhardt EJ, Parkin DM. *Rising Prostate Cancer Incidence in Sub-Saharan Africa: A Trend Analysis of Data from the African Cancer Registry Network*. *Cancer Epidemiol Biomarkers Prev*. 2021 Jan;30(1):158-165. doi: 10.1158/1055-9965.EPI-20-1005. Epub 2020 Oct 8. PMID: 33033143.

134 Horwich A, Hugosson J, de Reijke T, Wiegel T, Fizazi K, Kataja V; Panel Members; European Society for Medical Oncology. *Prostate cancer: ESMO Consensus Conference Guidelines 2012*. *Ann Oncol*. 2013 May;24(5):1141-62. doi: 10.1093/annonc/mds624. Epub 2013 Jan 9. PMID: 23303340.

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

136 <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>

137 <https://www.medsdal.org/?product%5B%5D=Enzalutamide+40mg&page=1>

will continue selling the generic version of the drug. Secondary patent on amorphous enzalutamide & solid compositions was filed in few LMICs and is expected to expire in 2033.

6.7.3 Darolutamide (Bayer); Apalutamide (Janssen)

Indication

Darolutamide and apalutamide are androgen receptor inhibitors similar to enzalutamide. Darolutamide, currently approved for non-metastatic castration-resistant prostate cancer, significantly lowers, by 31%, the risk of death compared to placebo¹³⁸. Recent data using darolutamide in a combination therapy shows a reduction in mortality by 32.5% among patients with metastatic, hormone-sensitive prostate cancer¹³⁹. 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 in combination with other androgen deprivation therapy (ADT) in non-metastatic¹⁵⁶ and metastatic disease¹⁵⁷.

Apalutamide showed improved progression-free survival and overall survival at 24 months compared to placebo plus other androgen deprivation therapy¹⁴⁰. Addition of apalutamide to ADT also showed improved quality of life, compared to ADT+ placebo¹⁴¹.

Patent status in LMICs

Primary patent expiry for darolutamide 2030; and for apalutamide 2027.

6.7.4 Sotorasib (Amgen)

Indication

Treatment of KRAS-mutated non-small cell lung cancer (NSCLC) following prior therapy.

Clinical relevance

2.2 million incident cases of lung cancer were reported in 2020 and more than 80% are classified as non-small cell cancers (NSCLC). Activating mutations in Kirsten rat sarcoma viral oncogene homologue (KRAS) are found in 25 to 30% of non-squamous-cell NSCLCs¹⁴². Sotorasib is a specific, irreversible inhibitor of the GTPase protein, KRAS^{G12C}. A recently published phase III clinical trial compared the efficacy and safety of sotorasib to standard therapy (Docetaxel) in patients with KRAS^{G12C}-mutated non-small cell lung cancer who had previously been treated with other anticancer drugs. The study showed that sotorasib offered a consistent advantage in terms of progression-free survival and overall response rate over docetaxel¹⁴³. These results reinforce the promising

138 Fizazi K, Shore N, Tammela TL, Ulys A, Vjaters E, Polyakov S, Jievaltas M, Luz M, Alekseev B, Kuss I, Le Berre MA, Petrenciu O, Snapir A, Sarapohja T, Smith MR; ARAMIS Investigators. [Nonmetastatic, Castration-Resistant Prostate Cancer and Survival with Darolutamide](#). *N Engl J Med*. 2020 Sep 10;383(11):1040-1049. doi: 10.1056/NEJMoa2001342. PMID: 32905676.

139 Smith MR, Hussain M, Saad F, Fizazi K, Sternberg CN, Crawford ED, Kopyltsov E, Park CH, Alekseev B, Montesa-Pino Á, Ye D, Parnis F, Cruz F, Tammela TLJ, Suzuki H, Utriainen T, Fu C, Uemura M, Méndez-Vidal MJ, Maughan BL, Joensuu H, Thiele S, Li R, Kuss I, Tombal B; ARASENS Trial Investigators. [Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer](#). *N Engl J Med*. 2022 Mar 24;386(12):1132-1142. doi: 10.1056/NEJMoa2119115. Epub 2022 Feb 17. PMID: 35179323.

140 Chi KN, Agarwal N, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, Juárez Soto Á, Merseburger AS, Özgüroğlu M, Uemura H, Ye D, Deprince K, Naini V, Li J, Cheng S, Yu MK, Zhang K, Larsen JS, McCarthy S, Chowdhury S; TITAN Investigators. [Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer](#). *N Engl J Med*. 2019 Jul 4;381(1):13-24. doi: 10.1056/NEJMoa1903307. Epub 2019 May 31. PMID: 31150574.

141 Agarwal N, McQuarrie K, Bjartell A, Chowdhury S, Pereira de Santana Gomes AJ, Chung BH, Özgüroğlu M, Juárez Soto Á, Merseburger AS, Uemura H, Ye D, Given R, Cella D, Basch E, Miladinovic B, Deprince K, Naini V, Lopez-Gilitz A, Chi KN; TITAN Investigators. [Health-related quality of life after apalutamide treatment in patients with metastatic castration-sensitive prostate cancer \(TITAN\): a randomised, placebo-controlled, phase 3 study](#). *Lancet Oncol*. 2019 Nov;20(11):1518-1530. doi: 10.1016/S1470-2045(19)30620-5. Epub 2019 Sep 29. PMID: 31578173.

142 Skoulidis F, Li BT, Dy GK, Price TJ, Falchook GS, Wolf J, Italiano A, Schuler M, Borghaei H, Barlesi F, Kato T, Curioni-Fontecedro A, Sacher A, Spira A, Ramalingam SS, Takahashi T, Besse B, Anderson A, Ang A, Tran Q, Mather O, Henary H, Ngarmchamnannrith G, Friberg G, Velcheti V, Govindan R. [Sotorasib for Lung Cancers with KRAS p.G12C Mutation](#). *N Engl J Med*. 2021 Jun 24;384(25):2371-2381. doi: 10.1056/NEJMoa2103695. Epub 2021 Jun 4. PMID: 34096690.

143 de Langen AJ, Johnson ML, Mazieres J, Dingemans AC, Mountziou G, Pless M, Wolf J, Schuler M, Lena H, Skoulidis F, Yoneshima Y, Kim SW, Linardou H, Novello S, van der Wekken AJ, Chen Y, Peters S, Filip E, Solomon BJ, Ramalingam SS, Dooms C, Lindsay CR, Ferreira CG, Blais N, Obiozor CC, Wang Y, Mehta B, Varrieur T, Ngarmchamnannrith G, Stollenwerk B, Waterhouse D, Paz-Ares L; CodeBreak 200 Investigators. [Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with KRASG12C mutation: a randomised, open-label, phase 3 trial](#). *Lancet*. 2023 Mar 4;401(10378):733-746. doi: 10.1016/S0140-6736(23)00221-0. Epub 2023 Feb 7. PMID: 36764316.

results in both treatment-experienced and treatment-naïve patients from the Phase I study that led to the FDA's accelerated approval of sotorasib for the treatment of KRAS G12C-mutated non-small cell lung cancer (NSCLC)¹⁴⁴.

Access in LMICs

The originator, Amgen, joined the Access To Oncology Medicines, ATOM, coalition, since its launch, in May 2022. This global initiative, convened by the Union for International Cancer Control, with several civil societies, public, and private sector partners (including the Medicines Patent Pool), aims to provide coordinated efforts towards the provision of comprehensive cancer care in LMICs, including strengthening the supply chain, capacity building, advocacy, demand generation, and training.

Patent status in LMICs

Primary patent expiry for sotorasib 2038.

Sotorasib compound patent was filed with a wide geographical scope, including in LMICs and is expected to expire in 2038. Several secondary patents on crystalline forms and processes are expected to expire between 2039 and 2040.

6.7.5 Adagrasib (Mirati Therapeutics)

Indication

Treatment of KRAS-mutated non-small cell lung cancer (NSCLC) following prior therapy.

Clinical performance

Adagrasib shows favourable safety profile and led to durable clinical benefit in KRAS^{G12C}-mutated NSCLC patients previously treated¹⁴⁵. Adagrasib also exhibited antitumour activity in patients with advanced solid tumours harbouring the KRAS^{G12C} mutation¹⁴⁶.

Access in LMICs

The actual access plans for LMICs are not clear at present.

Patent status in LMICs

Adagrasib compound patents filed in few LMICs with an expected expiry in 2038.

6.7.6 Oral paclitaxel / encequidar; Oral docetaxel / encequidar (Athenex)

Indication

The IV formulations of paclitaxel and docetaxel are on the EML, indicated for multiple solid tumours. The oral formulations are currently under study for metastatic breast cancer (both) and metastatic prostate cancer (docetaxel).

144 <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-sotorasib-kras-g12c-mutated-nsclc>

145 Jänne PA, Riely GJ, Gadgeel SM, Heist RS, Ou SI, Pacheco JM, Johnson ML, Sabari JK, Leventakos K, Yau E, Bazhenova L, Negrao MV, Pennell NA, Zhang J, Anderes K, Der-Torossian H, Kheoh T, Velastegui K, Yan X, Christensen JG, Chao RC, Spira AI. [Adagrasib in Non-Small-Cell Lung Cancer Harboring a KRASG12C Mutation](#). *N Engl J Med*. 2022 Jul 14;387(2):120-131. doi: 10.1056/NEJMoa2204619. Epub 2022 Jun 3. PMID: 35658005.

146 Ou SI, Jänne PA, Leal TA, Rybkin II, Sabari JK, Barve MA, Bazhenova L, Johnson ML, Velastegui KL, Cilliers C, Christensen JG, Yan X, Chao RC, Papadopoulos KP. [First-in-Human Phase I/IB Dose-Finding Study of Adagrasib \(MRTX849\) in Patients With Advanced KRASG12C Solid Tumors \(KRYSTAL-1\)](#). *J Clin Oncol*. 2022 Aug 10;40(23):2530-2538. doi: 10.1200/JCO.21.02752. Epub 2022 Feb 15. PMID: 35167329.

Clinical performance

A phase III study showed that oral paclitaxel plus encequidar increased confirmed tumour response compared with IV paclitaxel, with trends in PFS and OS¹⁴⁷. The FDA had raised concerns on the increase in neutropenia-related sequelae associated with oral paclitaxel/encequidar, as well as some aspects of the study design¹⁴⁸. The originator will re-engage the FDA by amending its NDA for metastatic breast cancer with recent data that further characterises the safety profile of oral paclitaxel¹⁴⁹.

Docetaxel has shown to be well-tolerated, and have acceptable bioavailability, PK characteristics similar to IV formulation¹⁵⁰.

As both drugs are oral formulations, they provide ease of administration. Further, the IV formulations are indicated for multiple solid tumours and included in the EML – the potential of multiple indications and lack of extra diagnostics makes these drugs particularly suited for the LMIC context.

Access in LMIC

The actual access plans for LMICs are not clear at present.

Patent status in LMICs

Paclitaxel and docetaxel compounds are both off patent. Patents covering taxane oral formulations (docetaxel or paclitaxel) filed and granted to Hanmi in many LMICs with the expected expiry date 20.03.2035. Encequidar compound patent is expected to expire on 07.10.2024. Patents on encequidar solid dispersions broadly filed in LMICs with an expected expiry in 12.12.2033.

6.7.7 Trastuzumab subcutaneous (Roche)

Indication

Trastuzumab is part of the adjuvant treatment of HER-2 overexpressing breast cancer. Trastuzumab is indicated as first-line treatment in combination with paclitaxel for metastatic HER-2 overexpressing breast cancer and as monotherapy in patients who have previously received one or more chemotherapy regimens in the metastatic setting¹⁵¹.

Clinical performance

One-year treatment with trastuzumab following adjuvant chemotherapy improves disease-free survival significantly in women with HER2-positive breast cancer^{152,153}. Subcutaneous administration of trastuzumab resulted in non-inferior levels of trastuzumab in the blood and non-inferior clinical efficacy compared to intravenous trastuzumab¹⁵⁴. The safety and tolerability were consistent with the known safety profiles of

147 Rugo HS, Umanson GA, Barrios FJ, Vasallo RH, Chivalan MA, Bejarano S, Ramirez JR, Fein L, Kowalyszyn RD, Kramer ED, Wang H, Kwan MR, Cutler DL; Oraxol Study Consortium Investigators. [Open-Label, Randomized, Multicenter, Phase III Study Comparing Oral Paclitaxel Plus Encequidar Versus Intravenous Paclitaxel in Patients With Metastatic Breast Cancer](#). *J Clin Oncol*. 2023 Jan 1;41(1):65-74. doi: 10.1200/JCO.21.02953. Epub 2022 Jul 20. PMID: 35858154.

148 <https://ir.athenex.com/news-releases/news-release-details/athenex-receives-fda-complete-response-letter-oral-paclitaxel>

149 <https://ir.athenex.com/news-releases/news-release-details/athenex-announces-mhra-decision-oral-paclitaxel>

150 https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.5050

151 <https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline/her2-positive-breast-cancer/her2-positive-breast-cancer>

152 Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, Gianni L, Baselga J, Bell R, Jackisch C, Cameron D, Dowsett M, Barrios CH, Steger G, Huang CS, Andersson M, Inbar M, Lichinitser M, Láng I, Nitz U, Iwata H, Thomssen C, Lohrisch C, Suter TM, Rüschoff J, Suto T, Grotzer V, Ward C, Straehle C, McFadden E, Dolci MS, Gelber RD; Herceptin Adjuvant (HERA) Trial Study Team. [Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer](#). *N Engl J Med*. 2005 Oct 20;353(16):1659-72. doi: 10.1056/NEJMoa052306. PMID: 16236737.

153 Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja E, Castro G Jr, Untch M, Smith I, Gianni L, Baselga J, Al-Sakaff N, Lauer S, McFadden E, Leyland-Jones B, Bell R, Dowsett M, Jackisch C; [Herceptin Adjuvant \(HERA\) Trial Study Team. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant \(HERA\) trial](#). *Lancet*. 2017 Mar 25;389(10075):1195-1205. doi: 10.1016/S0140-6736(16)32616-2. Epub 2017 Feb 17. Erratum in: *Lancet*. 2019 Mar 16;393(10176):1100. PMID: 28215665.

154 Jackisch C, Hegg R, Stroyakovskiy D, Ahn JS, Melichar B, Chen SC, Kim SB, Lichinitser M, Staroslawska E, Kunz G, Falcon S, Chen ST, Crepelle-Fléchaix A, Heinzmann D, Shing M, Pivot X. [HannaH phase III randomised study: Association of total pathological complete response with event-free survival in HER2-positive early breast cancer treated with neoadjuvant-adjuvant trastuzumab after 2 years of treatment-free follow-up](#). *Eur J Cancer*. 2016 Jul;62:62-75. doi: 10.1016/j.ejca.2016.03.087. Epub 2016 May 20. PMID: 27208905.

intravenous trastuzumab¹⁵⁵. The use of trastuzumab subcutaneous has been associated with cost savings and reduced chair time, being especially suitable for public health systems¹⁵⁶.

Access in LMICs

The originator, Roche, is involved in several broad access programs aimed at improving cancer care through comprehensive capacity-building and health system-strengthening activities in LMICs. It joined the Access To Oncology Medicines, ATOM, coalition, since its launch, in May 2022, this global initiative, convened by the Union for International Cancer Control, with several civil societies, public, and private sector partners (including the Medicines Patent Pool), aims to provide coordinated efforts towards the provision of comprehensive cancer care in LMICs, including strengthening the supply chain, capacity building, advocacy, demand generation, and training. Trastuzumab/hyaluronidase-oysk, (Herceptin Hylecta™) was approved by the US FDA in 2019, has been filed for registration in 58 out of 108 LMICs assessed by the Access To Medicines Foundation (ATMF)¹⁵⁷. Country-specific access programs are ongoing to ensure access to more affordable trastuzumab subcutaneous in several LMICs, in Kenya, for example, it was recently included in the package of the National Health Insurance Fund¹⁵⁸.

Patent status in LMICs

Trastuzumab patents expired in 2012. Patents on the subcutaneous formulation filed and granted widely in LMICs with an expected expiry in 2030.

6.8 Detailed assessments of diabetes, cardiovascular and metabolic disorders conditions priorities

6.8.1 Empagliflozin (Boehringer Ingelheim); 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 glycaemic control in non-pregnant adults¹⁵⁹. In addition to glycaemic control, recent data has shown significant cardiovascular benefit¹⁶⁰ and renal benefits¹⁶¹, 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^{162,163}. Dapagliflozin has been approved to treat heart failure in patients with reduced ejection fraction, as well as patients with chronic

155 Gligorov J, Ataseven B, Verrill M, De Laurentiis M, Jung KH, Azim HA, Al-Sakaff N, Lauer S, Shing M, Pivot X; SafeHer Study Group. [Safety and tolerability of subcutaneous trastuzumab for the adjuvant treatment of human epidermal growth factor receptor 2-positive early breast cancer: SafeHer phase III study's primary analysis of 2573 patients](#). Eur J Cancer. 2017 Sep;82:237-246. doi: 10.1016/j.ejca.2017.05.010. Epub 2017 Jun 16. PMID: 28625777.

156 Cynthia Villarreal-Garza, Cristel De la O-Maldonado, Héctor Díaz-Pérez, Fernanda Mesa-Chavez, Marisol García-García, Servando Cardona-Huerta, and Omar Peña-Curiel. [Cost and time savings of subcutaneous trastuzumab \(SC-T\) in a public health system in Mexico](#). Journal of Clinical Oncology 2019 37:15_suppl, e18387-e18387

157 <https://accesstomedicinefoundation.org/resource/the-methodology-for-the-2022-access-to-medicine-index>

158 <https://www.africa.com/kenya-ministry-of-health-nhif-and-roche-sign-mous-that-will-provide-herceptin-subcutaneous-injection-to-patients-insured-by-the-nhif-in-kenya-without-copayment/>

159 https://cdn.who.int/media/docs/default-source/essential-medicines/2021-eml-expert-committee/applications-for-addition-of-new-medicines/a_29_sgl2.pdf?sfvrsn=35f1e4c8_4

160 McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohávek J, Böhm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozd J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjöstrand M, Langkilde AM; DAPA-HF Trial Committees and Investigators. [Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction](#). N Engl J Med. 2019 Nov 21;381(21):1995-2008. doi: 10.1056/NEJMoa1911303. Epub 2019 Sep 19. PMID: 31535829.

161 Rabizadeh S, Nakhjavani M, Esteghamati A. [Cardiovascular and Renal Benefits of SGLT2 Inhibitors: A Narrative Review](#). Int J Endocrinol Metab. 2019 Apr 22;17(2):e84353. doi: 10.5812/ijem.84353. PMID: PMC6628616.

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

163 <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.>

kidney disease, regardless of diabetes status¹⁶⁴. Canagliflozin is also approved to reduce the risk of major cardiovascular events and end stage kidney disease in adults with type 2 diabetes¹⁶⁵.

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 2027-2031¹⁶⁶. Empagliflozin patents expire in 2025 (with secondary patents in 2026-2034)¹⁶⁷.

6.9 Detailed assessment of RMNCH and haematological disorders priority

6.9.1 Heat-stable carbetocin (Ferring Pharmaceuticals)

EML indication

Carbetocin is included in the EML for Postpartum haemorrhage (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 developed PPH¹⁶⁸. Approximately 72,000 women die annually due to post-partum haemorrhage¹⁶⁹, globally, representing about one quarter of maternal deaths. More than 99% of deaths due to PPH occur in LMICs.

In 2018, WHO updated the Guideline on the Use of Uterotonics for the Prevention of Postpartum Haemorrhage 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”¹⁷⁰. 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 carry significant quality challenges. Both oxytocin and ergotamine require refrigeration at 2-8°C from manufacturer to end-user. However, this is often 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^{171,172}. Ergotamine is also contraindicated in patients with hypertensive disorders (including chronic hypertension and pregnancy-related hypertension, pre-eclampsia or eclampsia), making it less suitable for contexts where routine screening for hypertension disorders is not done/possible.

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

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

166 <https://www.medspal.org/?keywords=canag&page=1>

167 <https://www.medspal.org/?keywords=empa&page=1>

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

169 GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. [Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016](#). *Lancet*. 2017 Sep 16;390(10100):1211-1259. doi: 10.1016/S0140-6736(17)32154-2. Erratum in: *Lancet*. 2017 Oct 28;390(10106):e38. PMID: 28919117.

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

171 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 Dec;123(13):2076-2086. doi: 10.1111/1471-0528.13998. Epub 2016 Mar 22. PMID: 27006180.

172 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.

Misoprostol also presents many of the quality challenges of oxytocin described above, with up to 50% of samples non-compliant with the specifications applied¹⁷³.

Access in LMICs

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 oxytocin¹⁷⁴. 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 2031¹⁷⁵.

6.10 Detailed assessment of RMNCH and haematological disorders watchlist product

6.10.1 Voxelotor (Global Blood Therapeutics)

Indication

Voxelotor is indicated to treat haemolytic anaemia (excess breakdown of red blood cells) in patients aged 12 years and older who have sickle cell disease.

An estimated 305'000 children are born with sickle cell disease each year. 90% of the world's sickle cell population lives in three countries: Nigeria, Democratic Republic of the Congo, 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 Africa¹⁷⁶.

Clinical performance

Voxelotor resulted in rapid and durable improvements in haemoglobin concentrations maintained over 72 weeks and has potential to address the substantial morbidity associated with haemolytic anaemia in sickle cell disease^{177,178}. As Voxelotor has a different mechanism of action from standard of care (mostly hydroxyurea in LMIC), it can be additive to the standard of care, or used in refractory cases/intolerance¹⁷⁹.

Access in LMICs

The actual access plans for LMICs are not clear at present.

173 Bower J, Chinery L, Fleurent A, et al. [Quality testing of mifepristone and misoprostol in 11 countries](#). Research Square; 2022. DOI: 10.21203/rs.3.rs-1909585/v1.

174 <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>

175 <https://www.medsdal.org/?product%5B%5D=Carbetocin+100+mcg%2Fml&page=1>

176 Wastnedge E, Waters D, Patel S, Morrison K, Goh MY, Adeloje D, Rudan I. [The global burden of sickle cell disease in children under five years of age: a systematic review and meta-analysis](#). J Glob Health. 2018 Dec;8(2):021103. doi: 10.7189/jogh.08.021103. PMID: PMC6286674.

177 Vichinsky E, Hoppe CC, Ataga KI, Ware RE, Nduba V, El-Beshlawy A, Hassab H, Achebe MM, Alkindi S, Brown RC, Diuguid DL, Telfer P, Tsitsikas DA, Elghandour A, Gordeuk VR, Kanter J, Abboud MR, Lehrer-Graiwer J, Tonda M, Intondi A, Tong B, Howard J; [HOPE Trial Investigators. A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease](#). N Engl J Med. 2019 Aug 8;381(6):509-519. doi: 10.1056/NEJMoa1903212. Epub 2019 Jun 14. PMID: 31199090.

178 Howard J, Ataga KI, Brown RC, Achebe M, Nduba V, El-Beshlawy A, Hassab H, Agodoa I, Tonda M, Gray S, Lehrer-Graiwer J, Vichinsky E. [Voxelotor in adolescents and adults with sickle cell disease \(HOPE\): long-term follow-up results of an international, randomised, double-blind, placebo-controlled, phase 3 trial](#). Lancet Haematol. 2021 May;8(5):e323-e333. doi: 10.1016/S2352-3026(21)00059-4. Epub 2021 Apr 7. PMID: 33838113.

179 Ware, R. E., Brown, C., de Montalembert, M., Tonda, M., Tong, B., Hoppe, C., Lehrer-Graiwer, J.; Abboud, M. R. (2019). [Concomitant Hydroxyurea and Voxelotor: Results from the HOPE Study](#). Blood, (Supplement_1), 1003.

Patent in LMICS

Compound patent is expected to expire in 2032¹⁸⁰. It has been granted in India and other LMICs (including ARIPO).

¹⁸⁰ MPP, based on information from the US FDA Orange book.