Review of Latvia's Pricing and Reimbursement System and its Lists of Reimbursed Medicines

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July 2023

Introduction

This report has been prepared at the request of the Latvian Ministry of Health (MoH) to review Latvia's pricing and reimbursed system and the lists of medicines covered by its National Health Service (NHS) as well as to recommend potential ways in which they could be improved to advance access to essential and cost-effective novel medicines for the population.

The report updates the findings of the "Roadmap for Improving Access to Medicines in Latvia delivered by the World Health Organization Regional Office for Europe to the Latvian MoH in 2021", focusing on the following issues:

- pharmaceutical expenditure,
- public pharmaceutical expenditure vs health needs of the population,
- potential for further savings through reforming rules for pricing of medicines,
- out-of-pocket payments,
- access to essential and novel medicines,
- health technology assessment and
- reimbursement decision-making.

The report draws on limited literature covering developments in the sector over the last several years, Latvian pricing and reimbursement regulation (Order 899) and information available on the websites of the MoH, State Medicines Agency (SMA) and NHS, and interviews with MoH, SMA and NHS staff.

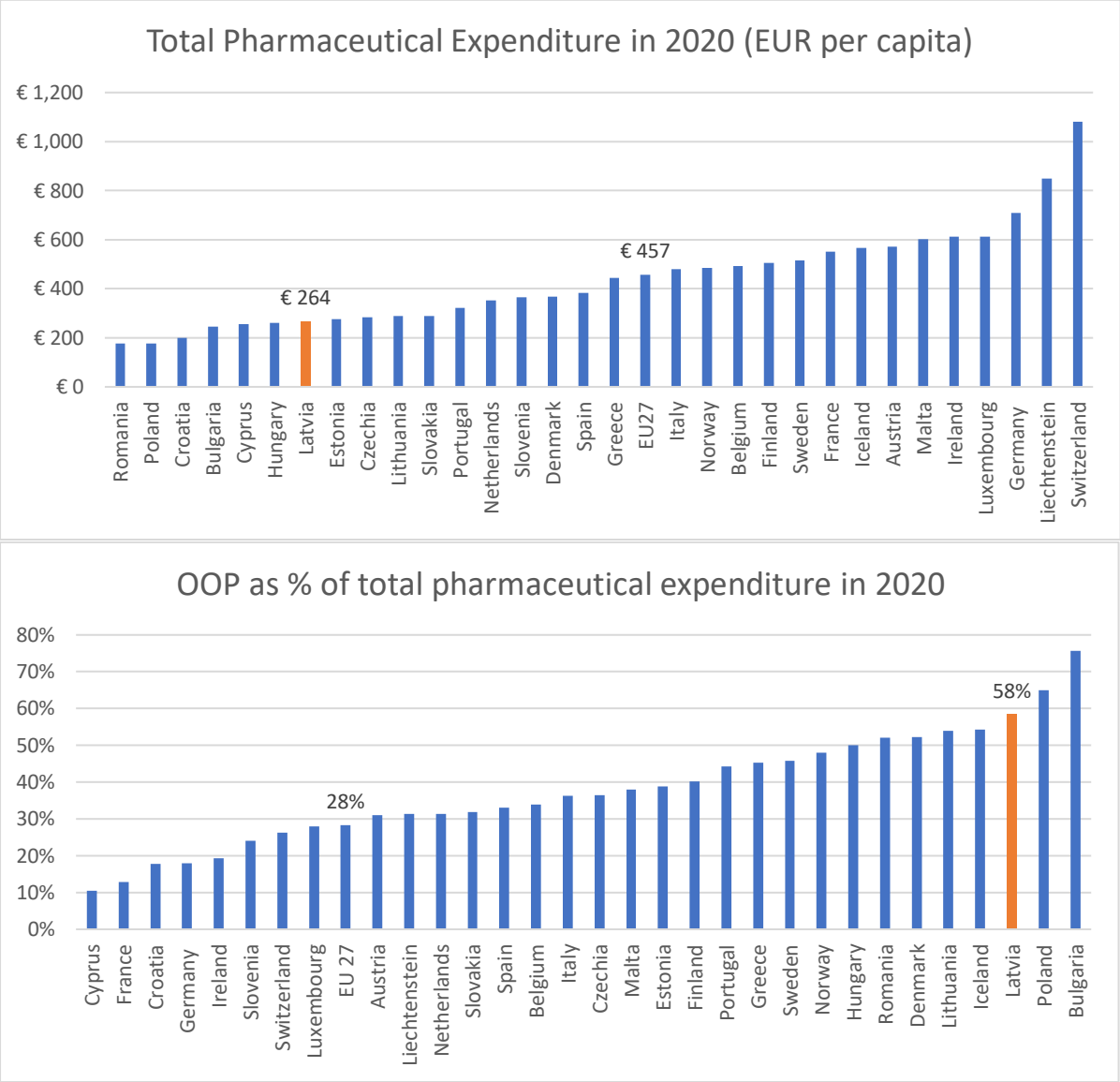
Acronyms

CHMP	Committee for Medicinal Products for Human Use
DDD	Defined daily dose
EMA	European Medicines Agency
GDP	Gross domestic product
HTA	Health technology assessment
INN	International non-proprietary name
MCDA	Multicriteria decision analysis
MoH	Ministry of Health
NHS	National Health Service
OOP	Out-of-pocket payment
PDD	Prescribed daily dose
PRIME	Priority medicines
SMA	State Agency of Medicines

Pharmaceutical expenditure

In absolute terms, and compared to other European countries, Latvia spends less on medicines per capita, and a disproportionately greater part of its pharmaceutical expenditure is financed by citizens through out-of-pocket (OOP) payments. In 2020, total pharmaceutical expenditure in Latvia reached EUR 264 per capita (58% of the EU 27 average), 58% of which (more than twice the average share in EU 27), was paid by patients out of pocket. Compared to other Baltic countries, Latvia spent the least amount on medicines per capita and had the highest share of private financing. In 2020, pharmaceutical expenditure in Lithuania reached EUR 288 and in Estonia it amounted to EUR 276, 54% and 39% of which respectively was paid by citizens out of pocket. See Figure 1 for more detail.

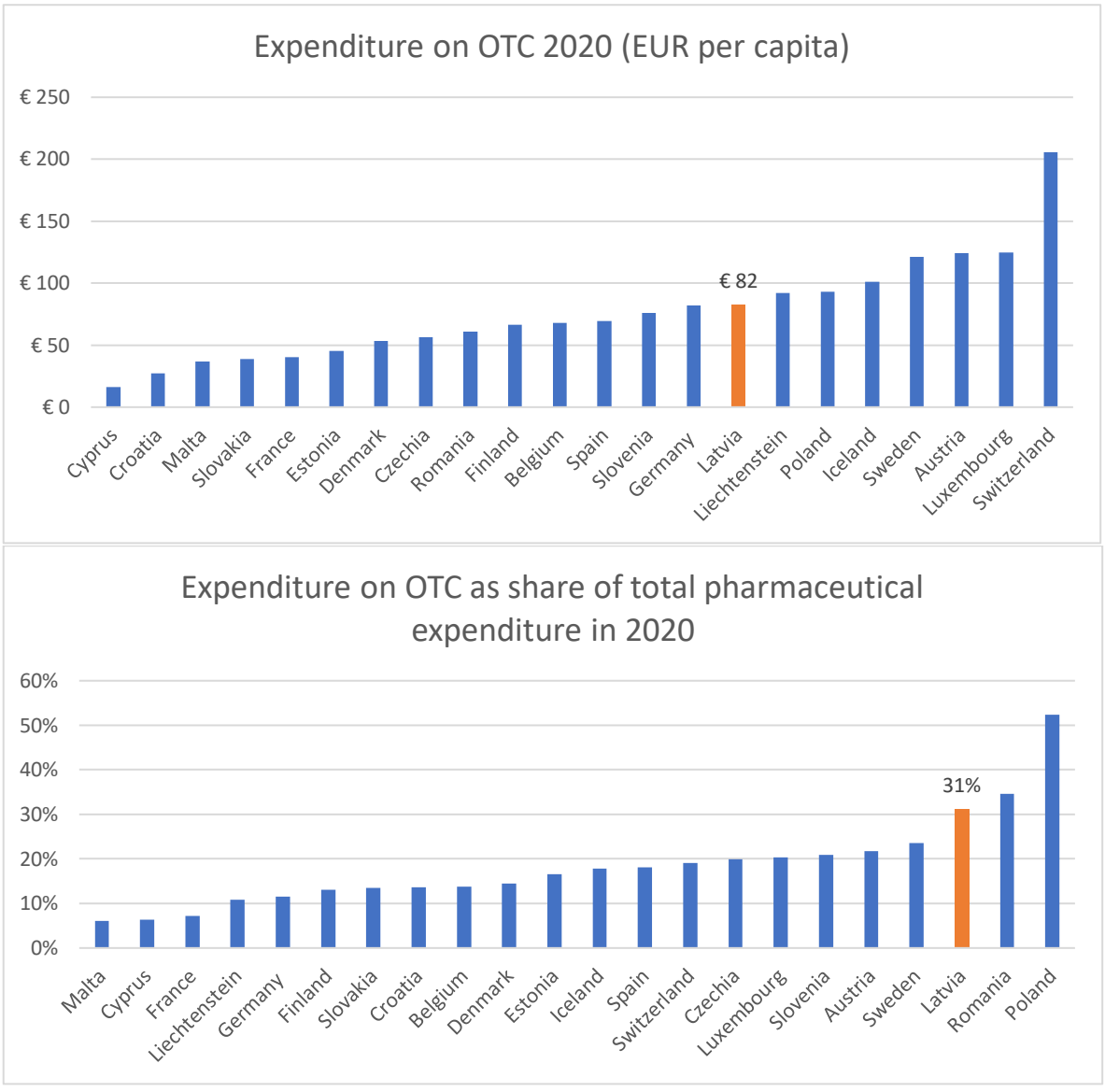
Figure 1- Total pharmaceutical expenditure in EUR and out of pocket payments as share of total pharmaceutical expenditure in 2020



Source: Eurostat 2023

At EUR 82 per capita, expenditure on over-the-counter medicines (OTC) in 2020 was higher than it was in most European countries, and it accounted for a much larger share of total pharmaceutical expenditure than it did in almost all European countries studied. The reasons for this need further exploration as it could be due to several factors including patient preferences, access to general practitioners/prescription medicines, categorisation of pharmaceuticals and high prices of OTCs. In 2020, other European countries (which reported data on OTC spending to Eurostat) spent on average EUR 76 per capita (EUR 68 if Switzerland and Lichtenstein are excluded). Expenditure on OTC in Latvia accounted for 31% of total pharmaceutical expenditure, almost double the average of European countries which reported data on OTC spending to Eurostat (18%) and higher than in all other countries except Bulgaria and Poland. See Figure 2 for more detail. With regards to other Baltic countries, Lithuania did not report on OTC expenditure to Eurostat, while in Estonia OTC expenditure reached EUR 46, which is 56% of the amount spent in Latvia on a per capita basis (Figure 2).

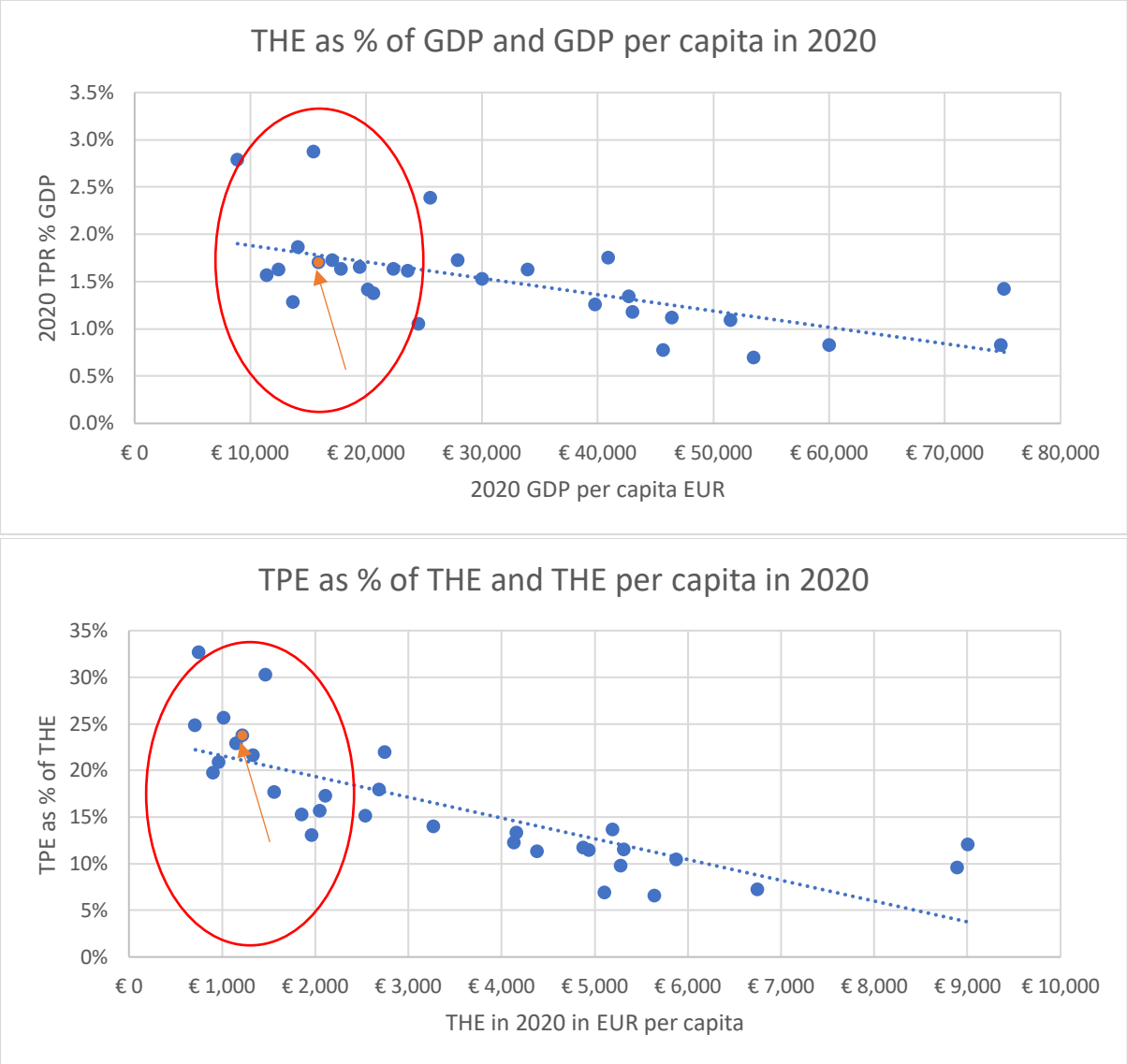
Figure 2 – Expenditure on OTC in EUR and as share of total pharmaceutical expenditure in 2020



Source: Eurostat 2023

In relative terms, compared to countries of similar economic development, Latvia spends slightly less on medicines expressed as share of GDP (including both public and private expenditure), while this spending accounts for a substantially larger share of its very modest health expenditure. In 2020, at 1,7%, total pharmaceutical expenditure (TPE) expressed as share of GDP fared slightly below the trendline of what other similarly developed countries spent, while pharmaceutical expenditure accounted for a larger share of Latvia's per capita health expenditure (23%). Other Baltic countries spent slightly less on medicines expressed as share of GDP (Lithuania 1,6% and Estonia 1,4%) and this translated to a slightly smaller share of their total health expenditure; 22% and 18% respectively (see Figure 3).

Figure 3- Total pharmaceutical expenditure as share of GDP vs GDP per capita and as share of total health expenditure vs total health expenditure per capita in 2020

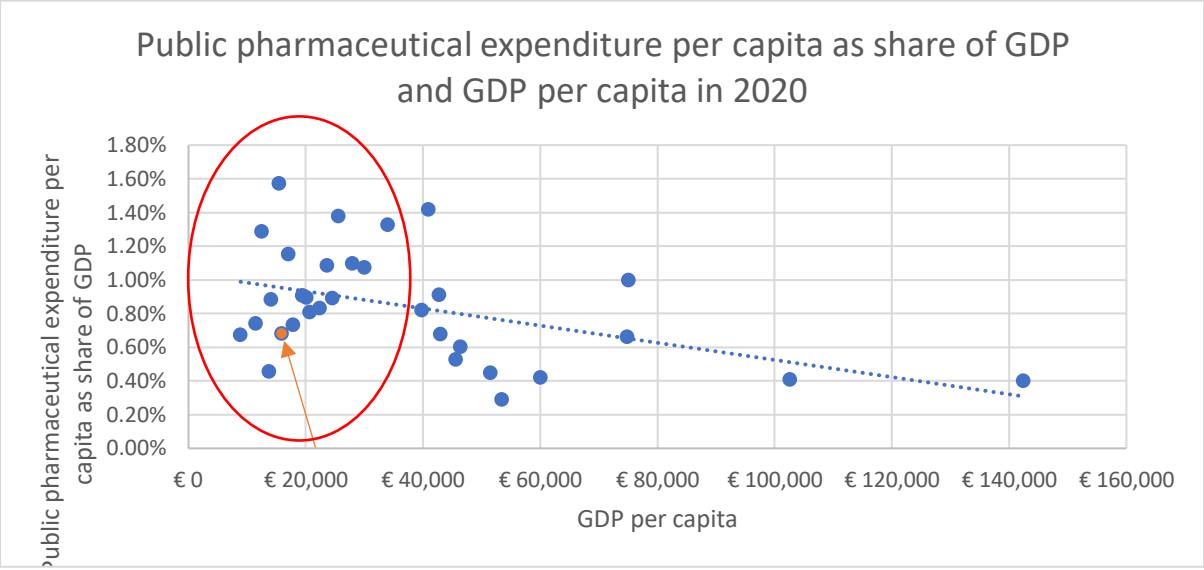


Source: Calculated based on Eurostat 2023

Public pharmaceutical expenditure vs health needs of the population and financial protection

However, if just the data on public pharmaceutical expenditure is considered, Latvia spends among the least of all European countries (expressed as share of GDP) of similar economic development, and this results in very high levels of out-of-pocket payments and catastrophic spending on health (in particular among the worst-off citizens) due to medicines. In 2020, public pharmaceutical expenditure in Latvia amounted to 0,68% of GDP. In the group of European countries with similar GDP, only Poland (0,45%) and Bulgaria (0,67%) spent less. Other Baltic countries also spent more as share of GDP: Lithuania 0,73% and Estonia 0,81% (see Figure 4). In 2013 (last data available), medicines accounted for around 55% of all out-of-pocket payments[1]. In 2016[2] (last data available), as many as 15% of Latvian households (284 000 people) experienced catastrophic levels of out-of-pocket spending on health, and medicines accounted for over 60% of this catastrophic spending. In Latvia, the incidence of catastrophic out-of-pocket spending is highly concentrated among the poorer quintiles of the population. In 2016, just over half of all households with catastrophic out-of-pocket payments were already very poor or at risk of impoverishment after out-of-pocket payments. The incidence of catastrophic spending on health is particularly heavily concentrated among pensioners. In 2013, nearly 30% of all pensioner households experienced catastrophic out-of-pocket payments; thus, 70% of all households with catastrophic spending were pensioner households.

Figure 4 – Public pharmaceutical expenditure as share of GDP vs GDP per capita in EUR in 2020

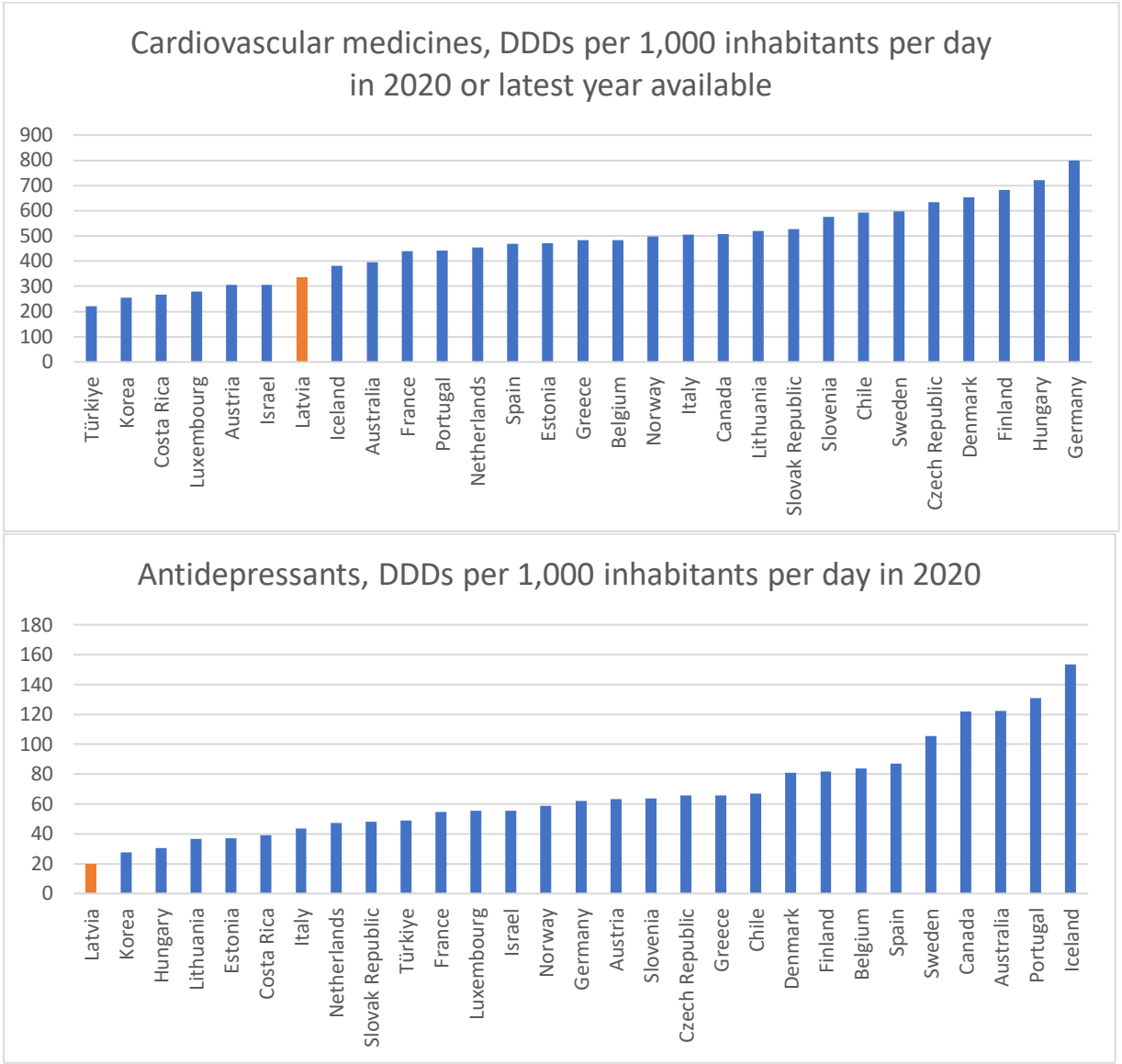


Source: Calculated based on Eurostat 2023

Available data on the usage of prescribed medicines, unmet needs for prescribed medicines and preventable and treatable mortality rates indicate that the public part of financing for medicines needs to be increased to meet the predicted needs of the Latvian population. In 2020 or latest year available, usage of some groups of prescribed medicines such as for instance cardiovascular drugs (336 Defined daily dose [DDDs] per 1.000 inhabitants per day) and antidepressants (20 DDD per 1.000

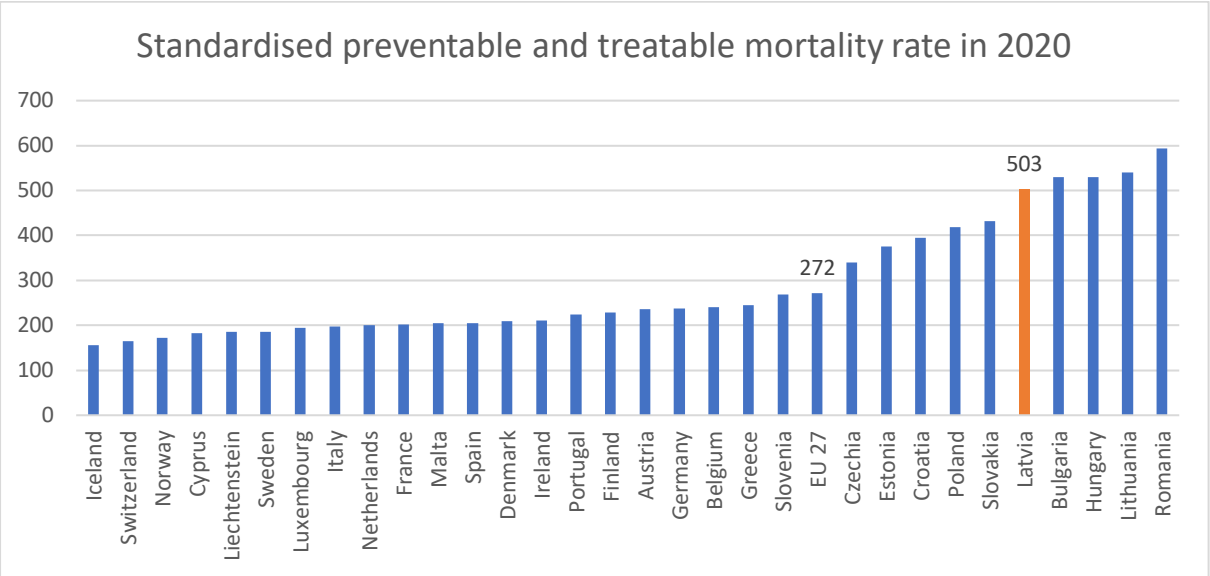
inhabitants per day) in Latvia was far lower than in most OECD countries and this is inconsistent with the epidemiologic profile of the population. Lithuania used 521 and Estonia 472 DDDs of cardiovascular medicines and both countries used 37 DDDs of antidepressants per 1.000 inhabitants per day. At 12%, the rate of self-reported unmet needs for prescribed medicines in 2019 because of financial reasons was the highest in Europe, and three times the EU 27 average of 4%. Estonia and Lithuania recorded 4% and 5%. The standardized preventable and treatable mortality rate in 2020 at 503 per 100.000 was 85% higher than the EU 27 average (272 per 100.000). Lithuania's rate was higher (540) while Estonia was lower (376). See figures 5 and 6 for more detail.

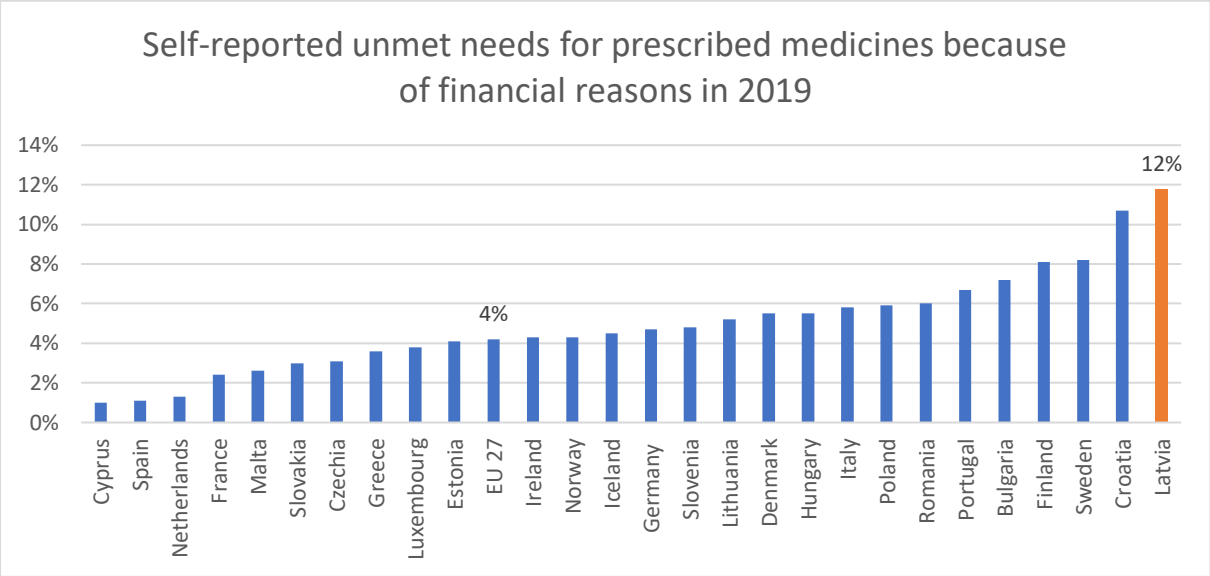
Figure 5 – Usage of cardiovascular medicines and antidepressants in 2020 or latest year available



Source: OECD 2023

Figure 6 – Standardised preventable and treatable mortality rate in 2020 and self-reported unmet needs for health care because of financial reasons in 2019.





Source: Eurostat 2023

It should be noted however that Latvia has since 2019 implemented a number of reform measures in pharmaceutical policy the effect of which is not yet captured by Eurostat data on unmet needs and preventable mortality rates. These include INN prescription, dispensing the cheapest version of generics, more funding for reimbursement, etc. Further research is required to understand the effect of these measures on the said indicators as well as on consumption of medicines measured in DDDs.

Potential for further savings through reforming rules for pricing of medicines

International price comparisons ensure low maximum allowed prices of medicines (prices are recalculated annually) (co)financed by the NHS by setting ex-factory[1] prices, which are then supplemented by regulated wholesale and retail mark-ups. The maximal allowed ex-factory price can't be higher than the third lowest price in the Czech Republic, Denmark, Romania, Slovakia, and Hungary (brand, prices of other brands of the same International non-proprietary name [INN] are not considered) and can't exceed its ex-factory price in Estonia and Lithuania. As the ex-factory price increases from EUR 1 to EUR 2,000, the regulated wholesale mark-up increases from EUR 0,1 to EUR 20 (decreasing as a share of the retail price, including VAT, from 6,25% to 0,88%) and the retail mark-up increases from EUR 0,33 to EUR 6,05 (decreasing as a share of the retail price, including VAT, from 20% to 0,27%) per pack of dispensed medicines[3].

Interchangeable medicines undergo internal reference pricing four times a year to further erode prices paid by the NHS, and this process is catalysed by listing of new generics which are subject to mandatory price decreases. Internal reference pricing groups are formed at the level of the INN or wider groups are used that comprise several INNs of similar therapeutic effect. The cheapest product based on defined (DDD) or prescribed daily dose (PDD, where applicable) daily doses sets the reference price and maximum acceptable co-payments are also regulated, implying delisting of medicines that would not reduce total prices to the allowed levels. If the reference product is permanently not available in the market, which needs to be confirmed by the Health Inspectorate, the reference price is raised to the second cheapest product. The first generic seeking reimbursement is subject to a mandatory 30% price decrease compared to the originator, the second and third generic to 10% price decreases compared to the last entry and all subsequent generic entrants are subject to 5% mandatory price decreases.

Progressive prescribing and dispensing rules introduced in 2020 force the use of cheapest interchangeable products (both the same INN and medicines considered to be therapeutically equivalent); these rules have been effective and have resulted in generics accounting for 74% of the volume of all dispensed products, some 20 percentage points over the OECD average[4]. The first time a drug is prescribed to a patient, the prescription needs to be in INN, and the cheapest product needs to be dispensed. Prescription by brand is allowed in subsequent prescriptions only "if the desired effect was not accomplished with the cheapest drug", but the patient needs to be informed of the co-payment. All prescriptions (except if marked "dispense as prescribed") are subject to mandatory substitution for the cheapest product. If the patient refuses mandatory substitution for a prescription that has not been marked "dispense as prescribed", the NHS does not reimburse any part of the price. Pharmacies need to stock all products listed in the reimbursement lists. If they are not available in the market, pharmacies need to notify the State Medicines Agency (SMA) within 24 hours.

There are mandatory price reductions for high growth non-interchangeable medicines and mandatory discounts for expensive medicines. The reimbursed prices of non-interchangeable medicines can be decreased if their volumes of sale grow for more than 10% compared to the previous year unless reimbursed indications have been widened. In case these products were listed more than three years ago, the pharmaceutical company is obliged to pay back all expenditure over the said limit.

[1] The price at which the manufacturer sells the product to the wholesaler.

For expensive medicines, pharmaceutical companies are obliged to enter into managed entry agreements that define volume/financial ceilings over which companies need to pay back all expenditure; with the minimal allowed pay back amounting to 10% of sales.

Access to essential and novel medicines

The list of covered outpatient medicines consists of five parts, while covered hospital medicines are defined through 14 lists that correspond to the main anatomical/ pharmacological groups of the ATC classification. Covered outpatient medicines are defined by brand name. The A list contains interchangeable products subject to reference pricing. The B list contains non interchangeable medicines which are not subject to reference pricing. The C list contains non interchangeable medicines, the cost of which surpasses EUR 4,268 per year, and which are subject to mandatory managed entry agreements which include volume/financial caps over which pharmaceutical companies must return revenues. The R list contains medicines for rare diseases. The M list contains medicines for pregnant and postpartum (70 days) women and children up to 24 months which are subject to high co-insurance rates of 75% (women) and 50% (children). Usage of C list and R list medicines needs to be approved on an individual patient basis by the NHS. Covered inpatient medicines are defined by international non-proprietary name (INN).

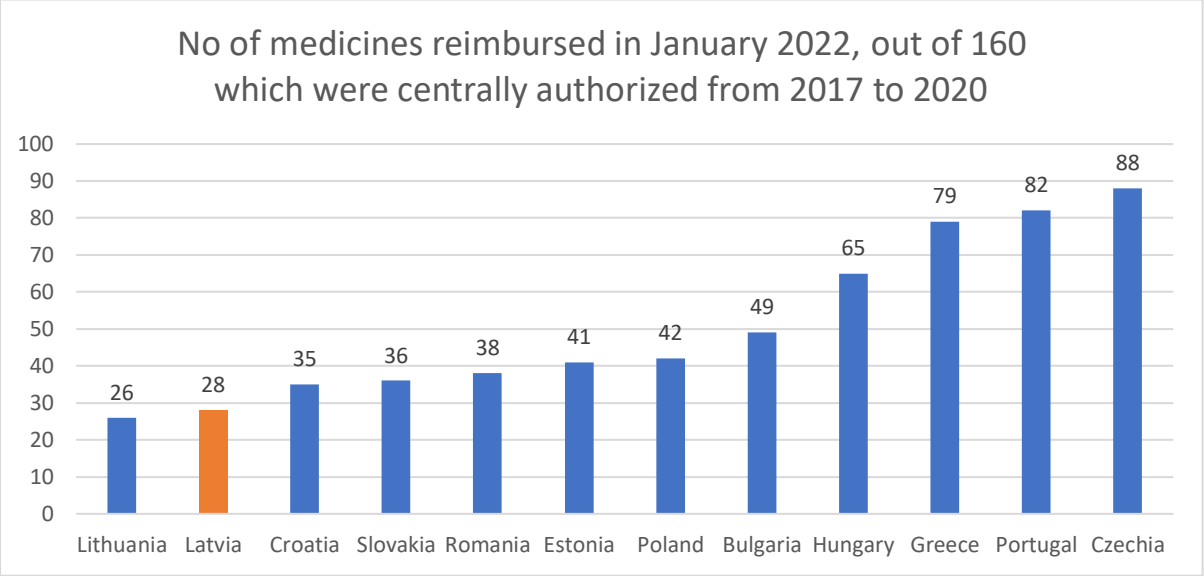
Compared to the World Health Organization's (WHO) 22nd model list of essential medicines (WHO EML 2021)[5], Latvia does not cover 114 of its 479 INNs (excluding medicines used for diagnostics, those for tropical diseases and medicines for Tuberculosis that are funded through a different program). According to the WHO, the Essential Medicines satisfy the priority health care needs of a population and are selected with due regard to disease prevalence and public health relevance, evidence of efficacy and safety and comparative cost-effectiveness. It can be anticipated that there will be differences between the Latvian reimbursement list and the EML as the model list is intended as a guide for countries to adopt or adapt in accordance with local priorities and treatment guidelines for the development and updating of national essential medicines lists. A strategy used by many countries is to select a limited number of essential medicines as essential, taking into consideration national disease burden and clinical need, and this can lead to improved access through streamlined procurement and distribution of quality-assured medicines, support more rational or appropriate prescribing and use and lower costs for both health care systems and for patients[6].

An analysis of the WHO EML 2021 identified 114 medicines that are not reimbursed in Latvia. For most there were clinically equivalent alternatives in the Latvian lists. There were other examples which would be less relevant to the Latvian context compared to other parts of the world with different economic circumstances and epidemiology. However, the analysis indicated that a number of them could be considered for reimbursement in Latvia. Most of these medicines are very old off-patent molecules (over a third are antibiotics, antifungals, and antivirals) which may not be sufficiently attractive for marketing to the pharmaceutical industry because of low expected volumes in Latvia and the strict pricing, prescribing and dispensing rules in place. Some of the more novel and expensive medicines listed in the WHO EML are also missing and should be considered for reimbursement (Box 1). The complete list of missing products is available in the annex.

Box 1 - Novel (more expensive) medicines not covered in Latvia which are listed in the WHO EML 2021	
INN	**WHO EML 2021 indication**
certolizumab pegol	Axial spondyloarthritis Crohn disease site Juvenile idiopathic arthritis Rheumatoid arthritis
arsenic trioxide	Acute myeloid leukaemia with recurrent genetic abnormalities
enzalutamide	Malignant neoplasms of prostate
pegaspargase	Lymphoid leukaemia, not elsewhere classified

With regards to novel medicines, according to the 2021 European Federation of Pharmaceutical Industries and Associations (EFPIA) W.A.I.T. survey[7], there were 160 medicines[2] authorized for use in the EU through the centralized procedure from 2017 to 2020; Latvia had in January 2022 reimbursed only 28, second lowest in a group of European countries with similar economic development. The most timely and comprehensive dataset on the availability of novel medicines across Europe is published by EFPIA. It comments on the availability of novel medicines authorised by EMA from 2017 to 2020 (160 in total), as of January 1, 2022. All European countries with GDP per capita under EUR 21.000 in 2020, except Lithuania, reimbursed more novel products than Latvia, most of the countries substantially so. See Figure 7 for more detail.

Figure 7 – Number of medicines centrally authorized from 2017 to 2020 in January 2022 which are reimbursed in Latvia and European countries of similar economic development



Source: EFPIA 2022

[2] It is important to note that not all of these would be considered of clinical and economic value or be aligned with the priority needs of the population in Latvia. Further, the W.A.I.T. analysis does not entail any information on the prices at which these medicines are sold in the countries nor makes any adjustment for purchasing power.

In April 2023, most of the medicines authorized under EMA's PRIority MEdicines (PRIME) scheme[3] which was set up in March 2016 to provide early and enhanced scientific and regulatory support to medicines that have the potential to significantly address patients' unmet medical needs were not reimbursed in Latvia. PRIME medicines represent significant progress in their therapeutic areas. They include innovative technologies such as the first CAR T-cell therapies to be authorised, one-time potentially curative gene therapies, rare cancer treatments and a vaccine for the Ebola virus. In the period from 7 March 2016 to 30 June 2021, 24 PRIME products were submitted for marketing authorisation, of which 21 concluded the MAA procedure of which 18 with positive opinions (of which 1 was the Ebola Vaccine which was excluded from analysis). See Table 1 for the full list of PRIME medicines.

Table 1 – PRIME medicines that received marketing authorization from 2019 to 2021

Brand name (INN)	Indication	Year of CHMP opinion	Reimbursed in Latvia
Abecma (Idecabtagene vicleucel)	Multiple myeloma	2020	
Blanrep (Belantamab mafodotin)	Multiple myeloma	2020	
Bylvay (Odevixibat)	Progressive familial intrahepatic cholestasis	2021	
Evrysdi (Risdiplam)	Spinal muscular atrophy	2021	Yes
Givlaari (Givosiran)	Acute hepatic porphyria	2020	
Hepcludex (Bulevirtide)	Chronic hepatitis delta virus (HDV) infection	2020	
Idefirix (Imlifidase)	Desensitisation treatment of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor	2019	
Imcivree (Setmelanotide)	Obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic proopiomelanocortin deficiency or biallelic leptin receptor deficiency	2021	
Kymriah (Tisagenlecleucel)	B-cell acute lymphoblastic leukaemia	2018	
Oxulmo (Lumasiran)	Primary hyperoxaluria type 1 (PH1) in all age groups	2020	
Polivy (Polatuzumab vedotin)	Diffuse large B-cell lymphoma	2019	Yes
Rozlytrek (Entrectinib)	Solid tumours that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion and ROS1-positive, advanced non-small cell lung cancer	2020	
Skysona (Elivaldogene autotemcel)	Early cerebral adrenoleukodystrophy	2021	
Tecartus (Autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral	Mantle cell lymphoma	2020	

[3] It is important to note that not all of these would be considered of clinical and economic value or be aligned with the priority needs of the population in Latvia.

vector expressing anti-CD19 CD28/ CD3-zeta chimeric antigen receptor and cultured)			
Yescarta (Axicabtagene ciloleucel)	Diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma	2018	
Zolgensma (Onasemnogene abeparvovec)	Spinal muscular atrophy	2020	
Zynteglo (Betibeglogene autotemcel)	Transfusion-dependent βthalassaemia	2019	

Patients are entitled to apply for public financing of medicines which are not included in the lists of reimbursed medicines; applications are assessed by the NHS on a case-to-case basis and can be approved up to a maximum annual amount per patient and up to a maximum annual amount for all patients in total. If the listed medicines are not sufficient for maintaining "vital functions" in a particular patient, the council of doctors of the health care institution (i.e., hospital) where the patient is treated can apply to the NHS to cover the cost of another treatment (subject to co-insurance rates determined by diagnoses). Approvals are granted for a 12-month period and, if in doubt, the NHS is allowed to request an additional evaluation by another council of doctors from another health care institution. The maximum amount that can be granted for an individual patient equals EUR 14.229 per year, and total expenditure on these treatments can't surpass 2% of annual NHS budgetary funds granted for reimbursement of all medicines. If treatment costs more than EUR 14.229, the remaining amount can be covered by the patient out-of-pocket or through a donation by the pharmaceutical company that markets the product. Medicines which have previously been turned down for reimbursement by the NHS are not eligible for this program.

Out-of-pocket payments

In addition to paying the full price of OTC medicines and prescription medicines which are not covered (if they can so afford), patients in Latvia are exposed to substantial co-payments for many medicines. Percentage co-payment rates of 25% and 50% apply depending on diseases for which the medicines are prescribed (with more severe illnesses generally benefiting from a high level of coverage), and modest fixed co-payments (prescription charges) at EUR 0,71 per prescription are charged for medicines which are 100% covered for a particular disease, except for products priced under EUR 4,27. Co-payments due to reference pricing are calculated as the difference in the price of a particular brand and the cheapest product available in the reference pricing group.

Very few citizens are exempted from large percentage co-payments (25% and 50%) on medicines and this only up to a defined expenditure ceiling, and, unlike with other types of care, there are no annual caps on co-payments for medicines. Children up to 18, households with an income below EUR 128 per family member per month and asylum seekers are the only categories of the population exempted from these co-payments. Exemptions apply only up to an amount of co-payments which

would have been paid of EUR 14,228 per year, after which patients need to pay co-payments as the general population[8].

HTA and reimbursement decision making

Health Technology Assessment (HTA), comprising of clinical and cost-utility evaluation, is undertaken by the SMA which forwards its recommendations for listing to the NHS. The SMA HTA department (4 staff in total) has 120 days to evaluate company proposals. Clinical evaluation focuses on comparative efficacy and national/ international treatment guidelines. Cost effectiveness is assessed based on models submitted by the industry considering confidential discounts under 2 separate ICER thresholds: 3 GDPs per capita for all medicines except those used to treat rare diseases where the threshold is set at an even higher level of EUR 300.000. SMA operates under the Baltic Guideline for economic evaluation of pharmaceuticals which (published in 2002 and currently under review in Estonia as it is considered outdated)[9] which is publicly available to guide submitters. Patient groups and associations of doctors are routinely formally invited to contribute to the process and the recommendations of the SMA are published on its website (except for price discounts which are confidential).

The NHS takes reimbursement decisions based on SMA recommendations, prioritizing medicines under a long set of nominal criteria, in practice primarily taking into account unmet needs, budget impact and overall availability of funding. The NHS department for medicines (5 staff in total of which 2 focus on reimbursement of novel medicines) has 60 days to reach decisions. Companies submit proposals that need to include budget impact analysis to the NHS (methodology not regulated in detail, e.g., the time period it needs to cover is not defined) and routinely negotiate reimbursement conditions further to the prices presented to the SMA which are used to establish cost-effectiveness of products. Firm requirements for reimbursement include the following: if a product is cost increasing, prescribing restrictions need to be defined, if therapy per patient costs more than EUR 4,268 per year, discounts over 10% are expected; and expenditure on all medicines needs to be kept within budget.

Text box 2: Criteria used in the prioritization of medicines for reimbursement[10]:

- Date when the proposal was submitted.
- Medical need elaborated as: unmet needs, position of the medicine in the treatment of the relevant disease, target group of patients.
- The therapeutic effectiveness of the drug compared to other available forms of treatment.
- Compliance with treatment regimens and international treatment guidelines.
- Evaluation carried out by other countries.
- Recommendations/priorities/opinion of professional associations of doctors regarding drug treatment priorities, the place of drugs in therapy and priority target groups of patients.
- Cost-effectiveness assessment according to the guidelines for the economic evaluation of medicines.
- Budget impact.

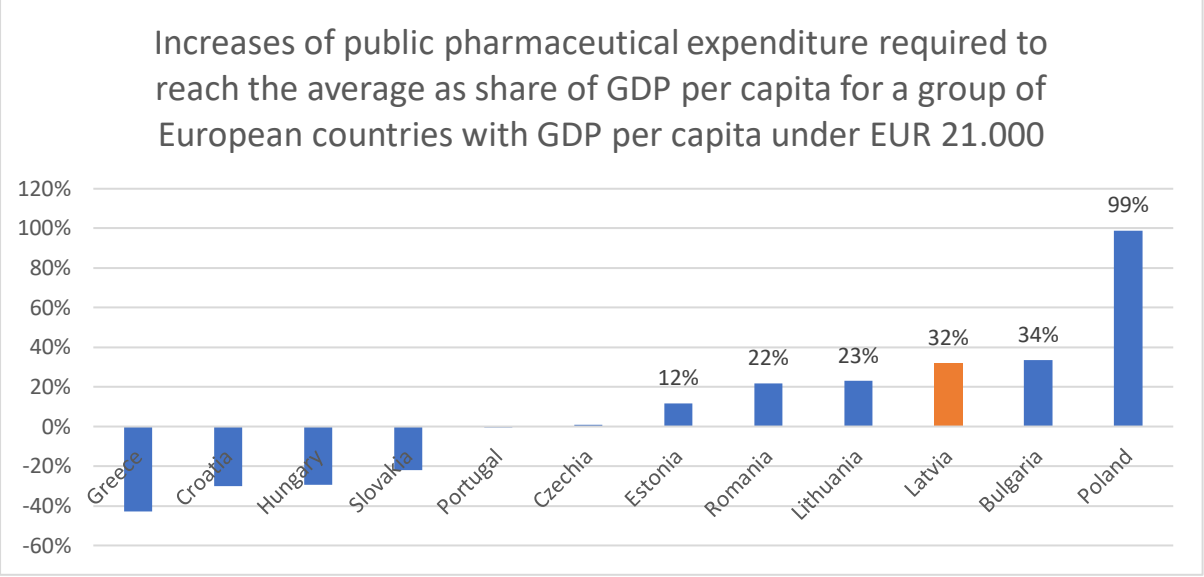
- Discount offered by the manufacturer.
- Number of points based on a prioritization tool that evaluates whether the disease is subject to a national screening program, preferences of specialists, stage of the disease (metastatic or non-metastatic and line of treatment), compliance with guidelines, the cost of treatment per year, confidential discount, impact on quality of life, overall survival, progression free survival and relative improvement in one-year or 5-year survival.

In 2022, the SMA positively assessed 49 medicines, and only 5 of these have been reimbursed up to May 2023 due to lack of budgetary funding for novel medicines. According to the NHS, of the total of 13 novel medicines reimbursed in 2022, some have been positively assessed and "waiting" for reimbursement for as long as a full decade. The analysis undertaken by WHO indicated that the funding dedicated for novel medicines is sufficient to reimburse only a minor fraction of medicines positively assessed by the SMA. This indicates that the current HTA rules and criteria used to prioritize these medicines need to be reviewed. Further, while the staff of the NHS Medicines department have to use the criteria elaborated in Text box 2 to prioritize medicines for reimbursement, there are no explicit rules on how individual medicines should be assessed against the large number of overlapping individual criteria or how the criteria should be weighed between each other.

Key Recommendations (update to recommendations issued in 2021)

1. Latvia would ned to increase its public budget for medicines by 32% to reach the average public expenditure on medicines as share of GDP for the group of European countries with GDP per capita under EUR 21.000. **WHO recommends Latvia to increase public financing for medicines to ensure better progress towards achieving Universal Health Coverage by improving access to essential and novel cost-effective medicines; which would also result in substantial positive effects on economic growth.** Universal health coverage means that all people and communities receive the health services (e.g. the full spectrum of health services from health promotion to prevention, treatment, rehabilitation, and palliative care across the life course) they need and of sufficient quality to be effective while also ensuring that the use of these services does not expose the user to financial hardship**.** Furthermore, it should not be forgotten that growth in healthcare investment has a clear relationship with economic growth as, among other reasons, long term illness is linked to employment, median income, and economic output. For example, a recent analysis from England showed that for each GBP 1 spend per head on the NHS, there is a corresponding return on investment of GBP 4[11].

Figure 8: Increases of public pharmaceutical expenditure required to reach the average as share of GDP per capita for a group of European countries with GDP per capita under EUR 21,000



Source: Calculated based on Eurostat 2023

2. **With regards to out-of-pocket payments for medicines, WHO recommends to direct additional budgetary financing primarily to decrease out-of-pocket payments for medicines for the most vulnerable populations (those with little capacity to pay), and those with large expenditures.** Ideally, health services and medicines should be affordable for all citizens at the point of use. However, given the extent and concentration of catastrophic spending in Latvia among the worst-off quintiles of the population[1,2] (particularly pensioner households) and the fact that substantial

increase of budgetary funds for medicines may take time, initial efforts should be targeted at the worst-off citizens who are at the greatest risk of catastrophic spending. The income ceiling of EUR 128 per family member per month used for exemptions from co-payments on medicines needs to be raised and effective implementation and uptake of this program needs to be ensured. In addition, an overall cap on out-of-pocket payments for prescription medicines needs to be put in place to protect all citizens with expenditure over a certain limit regardless of their income, as is the case for other types of care. Alternatively, Latvia could follow the example of Estonia which has recently introduced a rule that reduces co-payments above a certain limit.

3. **WHO also recommends Latvia to use additional budgetary financing to improve access to novel cost-effective treatments which are currently not accessible to the population.** Latvia lags substantially behind other countries of similar economic development in public financing of novel medicines. This has clear implications on the state of medical treatment and patient health outcomes. The current HTA system includes cost-utility assessment under ICER thresholds and guarantees that any additional expenditure on novel medicines will be cost-effective.

4. **While there is modest potential for further large price cuts on covered medicines, some savings (and in particular reductions in OOPs) could be accrued by reforming wholesale and retail markups in line with the conclusions of the "Roadmap for Improving Access to Medicines in Latvia delivered by the World Health Organization Regional Office for Europe to the Latvian Ministry of Health in 2021**

5. **WHO recommends Latvia to change reimbursement regulation to allow public stakeholders such as hospital committees for medicines and professional associations of doctors to propose off-patent essential medicines for reimbursement.** As demonstrated by the comparison of Latvian reimbursement lists with the WHO EML, a number of old and cheap medicines recommended by WHO are not publicly financed in Latvia. Listing these and potentially other off-patent medicines which are not costly and which would help cover unmet health needs would give a clear signal to the industry to start importing these products, and if this does not materialize, international procurement could be contemplated. The process could be administratively limited; e.g. to medicines which have had off-patent status for at least 10 years, which cover unmet health needs and where the cost of annual treatment does not surpass a certain amount. Requests would need to be well argued, but would not need to entail all information required for full HTA evaluation given that this channel of reimbursement would not be open to the pharmaceutical industry.

6. **WHO recommends Latvia to streamline prioritization criteria and the process in which they are used for reimbursement decision making and to align them with the EU HTA regulation (EU 2021/2282)[12].** As Latvia, all European countries take multiple criteria into account in reimbursement decision making. While the use of Multicriteria decision analysis (MCDA) as a decision support approach that would allow to take these criteria into account in an explicit, mathematical way has been discussed and advocated at length in the academia over the last decade[13,14], the concept has as of yet not taken root in real life decision making for reimbursement

of medicines at regional or national levels for a variety of reasons; with political concerns, and uncertainty and complexity inherent to reimbursement decisions tentatively being some of the larger challenges. For this reason, this report recommends the Latvian MoH to first reform its current lengthy and overlapping list of criteria and to better define the process in which they are to be used, and to consider using MCDA as an explicit prioritization tool at a later point in the future when more evidence on its use in real life decision making becomes available.

a. Criteria

To bring Latvia in alignment with other European member states, the Latvian MoH needs to reform its current long and overlapping list of decision criteria. It could be shorter (thus more fit for practical daily use), while making sure that the criteria are mutually exclusive and collectively exhaustive – fairly representing national values, citizens' preferences, and national policies. Table 2 presents criteria used for decisions on reimbursement recommended by a WHO consultative group as well as in several European countries[15], some of which could be adopted for decision making in Latvia. Table 3 presents a list that could be used as a starting point in the development of new Latvian criteria for reimbursement.

Table 2: Criteria used for decisions on reimbursement in European countries

WHO consultative group on equity and universal health coverage	• Cost-effectiveness • Priority to the worst off (with least health or the most severe and large individual disease burden) without the intervention or poorest or otherwise disadvantaged • Financial risk protection
France	• Severity of disease and impact on morbidity and mortality • Clinical efficacy, effectiveness, and safety • Reason for use (preventive, curative or symptomatic) • Therapeutic strategy in respect of alternatives • Impact on public health (burden of disease, community health, relevance of clinical trial results)
Italy	• Therapeutic characteristics (including relative value with standard of care) • Disease-specific criteria (severity of illness, size of target population, medical needs) • Results of clinical trials • Risk–benefit studies (comparison with existing therapies) • Cost–effectiveness analyses (often provided by manufacturers) • Cost in comparison with other interventions • Production methods and costs
Norway	• Health gain • Resource use • Severity of disease
Spain	• Absolute therapeutic value of the product with respect to the severity, duration and consequences of the condition, a clinical need, therapeutic and social value • Degree of innovation • Price in comparison with that of alternatives • Budget impact
Spain	• Cost–effectiveness (cost–utility) from a social perspective • Marginal benefit over alternative treatments • Severity of the disease • Unmet need for a new drug

	• Social criteria: vulnerability of patient groups, impact on equity and ethical dimensions
England, Ireland, and Wales	• Appropriateness and relevance in comparison with other technologies • Clinical effectiveness, risks, and health-related factors • Cost-effectiveness (cost, quality-adjusted life years) • Non-health factors (considered socially valuable)
Scotland	• Clinical effectiveness and risks • Cost-effectiveness (cost, quality-adjusted life years) • Budget impact
Slovenia[16]	• Alignment with public health priorities • Therapeutic value and relative therapeutic value • Cost-effectiveness • Budget impact • Ethical aspects (severe and rare conditions) • Assessment by independent sources (guidelines, WHO, other HTA agencies, etc.)
Croatia[17]	• Public health relevance • Therapeutic value • Relative therapeutic value • Ethical aspects (rare diseases only) • Price of treatment (vs comparators) • Budget impact • No of EU countries that reimburse the product

Table 3: Criteria that could be used as a starting point for discussions in the development of new Latvian criteria for reimbursement

Potential criterion	**Reporting performance**
Cost-effectiveness in Latvia	Incremental cost effectiveness ratio - ICER (range)
Budget impact	Monetary (minimum to maximum) on pharmaceutical budget and on total health system spending
Alignment with Government health priorities	Extent of alignment with legislation, national programs, screening programs, etc.
Burden of illness	Incidence, prevalence, morbidity, mortality, DALYs
Efficacy, effectiveness, and safety	Impact on final and intermediate health outcomes, certainty of evidence, etc.
Unmet health needs and relative effectiveness	Additional therapeutic benefit compared to current treatment
Ethical considerations	Rare diseases, end of life treatment, disadvantaged populations, child specific disease, etc.
Organizational feasibility	Technical and organizational aspects of the use of the new product
Alignment with international guidelines	Positioning of the product in European clinical guidelines
Percentage of EU countries that reimburse the product in the said indication	Percentage out of 27 EU Member States

b. Process

To improve transparency, the SMA could prepare succinct reports on the medicines proposed for reimbursement, containing key information on how they perform against the reimbursement criteria. An appraisal committee with permanent members free of conflict of interest (to ensure legitimacy, consistency in decision making as well as institutional memory) could review and discuss medicines accumulated in the substantial backlog of proposals that have been positively assessed by the SMA using these concise reports and rank products for reimbursement. The membership of the appraisal committee should be broad and representative of different fields of medicine to ensure some diseases are not prioritized for subjective reasons. For this process to work, each committee member will have to first (for him/herself) decide how the proposals perform in terms of the individual criteria. This should be straightforward and tentative scores could be prescribed when the criteria will be legislated. Weighing between the different criteria case by case (on their relative importance) and deciding how the criteria impact each other could be more complex, between the quantifiable and non-quantifiable criteria. The MoH could offer guidance or even regulate some aspects of this process, for instance by introducing several ICER thresholds to determine what is considered cost-effective. For instance, several European HTA agencies have set good examples of the use of structured deliberation in practice. The National Health Care Institute in the Netherlands applies a decision rule that relates "cost–effectiveness" to "severity of disease". Thus, the cost–effectiveness threshold is €80 000 per quality-adjusted life year for an intervention against a medical condition with a severity greater than 0.71 on a scale from 0 to 1 and less than €80 000 for less severe conditions[18]. In the United Kingdom, NICE uses a similar approach, which it refers to as "structured decision making", in which cost–effectiveness is traded-off quantitatively with the criteria "end of life" and "very rare disease", which are explicitly operationalized for this purpose. NICE also allows additional considerations to affect the overall recommendation[19]. The final ranking of proposals by the Appraisal committee can be undertaken by voting, members awarding points, the Delphi method or in a similar fashion. The process can in the future be repeated in regular intervals to decide on new reimbursements as industry proposals accumulate.

c. Staffing

Any improvements in HTA and reimbursement decision making will require strengthening of human resources at the SMA and NHS.

Annex - medicines listed in the WHO EML 2021 which are not reimbursed in Latvia [4]

Various diseases

acetic acid	Infectious diseases of external ear	S02AA10
Allopurinol	Gout Tumour lysis syndrome	M04AA01
Amiloride	Oedema, Ascites	C03DB01
anti-rabies immunoglobulin	Rabies	J06BB05
anti-rabies virus monoclonal antibodies	Rabies	
bisacodyl	Constipation	
bumetanide	Heart failure Anuria or oliguria Oedema	
caffeine citrate	Apnoea of new-born	N06BC01
canagliflozin	Type 2 diabetes mellitus	
carbachol	Primary open-angle glaucoma Acute angle closure with pupillary block Ocular hypertension	
carbimazole	Thyrotoxicosis	
chlortalidone	Essential hypertension Heart failure	
cyclizine	Palliative care	R06AE03
diazoxide	Persistent hyperinsulinaemic hypoglycaemia of infancy	V03AH01
dimercaprol	Harmful effects of or exposure to noxious substances, chiefly nonmedicinal as to source, not elsewhere classified	V03AB09
docusate sodium	Palliative care	A06AA02
dolasetron	Palliative care	
equine rabies immunoglobulin	Rabies	J06BB05
fexofenadine	Allergic or hypersensitivity conditions of unspecified type	
flunisolide	Asthma	
fomepizole	Harmful effects of or exposure to noxious substances, chiefly nonmedicinal as to source, not elsewhere classified	V03AB34
homatropine	Anterior uveitis	
hydralazine	Gestational hypertension	C02DB02
lovastatin	Mixed hyperlipidaemia Coronary atherosclerosis	
methylthioninium chloride	Acquired methaemoglobinaemia	V03AB17
oxycodone	Pain	
penicillamine	Rheumatoid arthritis, serology unspecified	M01CC01

[4] Clinically equivalent alternatives may be available

potassium ferric hexacyanoferrate	Harmful effects of or exposure to noxious substances, chiefly nonmedicinal as to source, not elsewhere classified	V03AB31
pravastatin	Mixed hyperlipidaemia	
terbutaline	Chronic obstructive pulmonary disease Asthma	
tetracaine	Local anaesthetics	S01HA03
tropisetron	Palliative care Nausea or vomiting	
vecuronium	Muscle relaxants	M03AC03
xylometazoline	Nasal congestion	R01AA07

Biologic medicines

certolizumab pegol	Axial spondyloarthritis Crohn disease site Juvenile idiopathic arthritis Rheumatoid arthritis	

Dermatology

selenium sulfide	Seborrhoeic dermatitis Pityriasis versicolor	D01AE13
sodium thiosulfate	Pityriasis versicolor	V03AB06
tacalcitol	Psoriasis of unspecified type	
podophyllotoxin	Warts	
benzoyl peroxide	Acne	D10AE01
calamine	Pruritus	D02AB
coal tar	Psoriasis of unspecified type	D05AA
terbinafine	Fungal infection of the skin	D01AE15

Vitamins

retinol	Vitamin A deficiency	A11CA01
riboflavin	Vitamin B2 deficiency	A11HA04
hydroxocobalamin	Megaloblastic anaemia due to vitamin B12 deficiency	B03BA03

Gynaecology

carbetocin	Postpartum haemorrhage	H01BB03

clomifene	Female infertility without specification whether primary or secondary	G03GB02
mifepristone - misoprostol	Induced abortion	G03XB01, G02AD06
misoprostol	Postpartum haemorrhage	G02AD06
norethisterone	Excessive menstruation with irregular cycle	
norethisterone enantate	Contact with health services for reasons associated with reproduction	G03AC01
ulipristal	Contact with health services for postcoital contraception	G03AD02

Mental health & Neurology

lithium carbonate	Bipolar or related disorders	N05AN01
biperiden	Parkinson disease	N04AA02
chlorpromazine	Schizophrenia or other primary psychotic disorders	N05AA01
ethosuximide	Absence seizures, typical	N03AD01
fluphenazine	Schizophrenia or other primary psychotic disorders	N05AB02
lorazepam	Status epilepticus	N05BA06
phenytoin	Epilepsy or seizures	N03AB02
propylthiouracil	Thyrotoxicosis	H03BA02
sumatriptan	Migraine	N02CC01

Cancer

daunorubicin	Acute myeloid leukaemia with recurrent genetic abnormalities	L01DB02
all-trans retinoic acid	Acute myeloid leukaemia with recurrent genetic abnormalities	L01XF01
arsenic trioxide	Acute myeloid leukaemia with recurrent genetic abnormalities	L01XX27
bendamustine	Follicular lymphoma	L01AA09
enzalutamide	Malignant neoplasms of prostate	
mesna	Osteosarcoma of bone and articular cartilage of other specified sites Other specified malignant neoplasms of the ovary Germ cell tumour of testis Ewing sarcoma of bone and articular cartilage of unspecified sites Rhabdomyosarcoma primary site Burkitt lymphoma including Burkitt leukaemia Malignant neoplasms of kidney, except renal pelvis	V03AF01
nilutamide	Malignant neoplasms of prostate	
pegaspargase	Lymphoid leukaemia, not elsewhere classified	L01XX24
rasburicase	Tumour lysis syndrome	V03AF07
thalidomide	Plasma cell myeloma	L04AX02

Antibiotics and antifungals

benzathine benzylpenicillin	Syphilis, Congenital syphilis [children]	J01CE08
azithromycin	Chlamydia trachomatis Paratyphoid fever Typhoid fever Gonococcal infection Trachoma Yaws Cholera Cholera [children] Infectious gastroenteritis or colitis without specification of infectious agent Gonococcal infection Trachoma	J01FA10
caspofungin	Systemic or invasive candidosis	
anidulafungin	Systemic or invasive candidosis	
cefiderocol	Carbapenem-resistant Pseudomonas aeruginosa Carbapenem resistant Enterobacterales	J01DI04
cefixime	Infectious gastroenteritis or colitis without specification of infectious agent Gonococcal infection	J01DD08
cefotaxime	Peritonitis (mild-moderate) Peritonitis (severe) Bacterial meningitis Other specified pneumonia (Hospital-acquired pneumonia) Inflammatory and other diseases of prostate (severe) Acute pyelonephritis (severe) Peritoneal abscess (mild-moderate) Peritoneal abscess (severe) Bacterial pneumonia (Community-acquired pneumonia - severe) [children] Bacterial pneumonia (Community-acquired pneumonia - severe) Bacterial infection of joint Osteomyelitis or osteitis Sepsis without septic shock Inflammatory and other diseases of prostate (mild to moderate) Acute pyelonephritis (mild to moderate)	J01DD01
ceftazidime + avibactam	Carbapenem-resistant Pseudomonas aeruginosa Carbapenem resistant Enterobacterales	J01DD52
chlortetracycline	Other specified conjunctivitis Infectious keratitis Trachoma Infectious blepharitis	
cloxacillin	Bacterial infection of joint Osteomyelitis or osteitis Bacterial cellulitis, erysipelas or lymphangitis Sepsis without septic shock	J01CF02
fosfomycin (injection)	Carbapenem-resistant Pseudomonas aeruginosa Carbapenem resistant Enterobacterales	J01XX01
kanamycin	Other specified conjunctivitis Infectious blepharitis	

linezolid	Methicillin resistant Staphylococcus aureus Vancomycin resistant Staphylococcus aureus Vancomycin resistant Enterococcus Multi-drug resistant Mycobacterium tuberculosis	J01XX08
meropenem + vaborbactam	Carbapenem resistant Enterobacterales Carbapenem-resistant Pseudomonas aeruginosa Carbapenem resistant Acinetobacter baumannii	J01DH52
micafungin	Systemic or invasive candidosis	J02AX05
miconazole	Fungal infection of the skin	D01AC02
natamycin	Infectious keratitis	S01AA10
netilmicin	Infectious blepharitis	
nystatin	Candidosis	A07AA02
oxytetracycline	Other specified conjunctivitis Infectious keratitis Trachoma Infectious blepharitis	
plazomicin	Carbapenem resistant Acinetobacter baumannii Carbapenem-resistant Pseudomonas aeruginosa Carbapenem resistant Enterobacterales	J01GB14
polymyxin B (injection)	Carbapenem resistant Enterobacterales Carbapenem resistant Acinetobacter baumannii Carbapenem-resistant Pseudomonas aeruginosa	J01XB02
spectinomycin	Gonococcal infection	J01XX04
tetracycline	Other specified conjunctivitis Infectious keratitis Trachoma Infectious blepharitis	S01AA09
trimethoprim	Infectious cystitis	J01EA01

TB (different procurement system, list not publicly available)

bedaquiline	Multi-drug resistant Mycobacterium tuberculosis	J04AK05
clofazimine	Multi-drug resistant Mycobacterium tuberculosis Leprosy	J04BA01
cycloserine	Multi-drug resistant Mycobacterium tuberculosis	J04AB01
delamanid	Multi-drug resistant Mycobacterium tuberculosis	J04AK06
ethambutol	Tuberculosis	J04AK02
ethambutol + isoniazid + pyrazinamide + rifampicin	Tuberculosis	J04AM06
ethambutol + isoniazid + rifampicin	Tuberculosis	J04AK02, J04AC01, J04AB02
ethionamide	Multi-drug resistant Mycobacterium tuberculosis	J04AD03
isoniazid	Tuberculosis	J04AC01
isoniazid + pyrazinamide + rifampicin	Tuberculosis	J04AM05

isoniazid + pyridoxine + sulfamethoxazole + trimethoprim	Other specified prophylactic measures	J04AC51
isoniazid + rifampicin	Tuberculosis	J04AM02
isoniazid + rifapentine	Latent tuberculosis	J04AC51
moxifloxacin	Multi-drug resistant Mycobacterium tuberculosis	J01MA14
p-aminosalicylic acid	Multi-drug resistant Mycobacterium tuberculosis	J04AA01
rifabutin	Tuberculosis	J04AB04
rifampicin	Tuberculosis	J04AB02
rifapentine	Tuberculosis	J04AB05
terizidone	Multi-drug resistant Mycobacterium tuberculosis	
streptomycin (injection)	Multi-drug resistant Mycobacterium tuberculosis	J01GA01

Antivirals

atazanavir + ritonavir[5]	Human immunodeficiency virus disease without mention of associated disease or condition, clinical stage unspecified	J05AR23
daclatasvir	Chronic hepatitis C	J05AP07
daclatasvir + sofosbuvir	Chronic hepatitis C	J05AP07, J05AP08
dasabuvir[6]	Chronic hepatitis C	J05AX16
efavirenz + lamivudine + tenofovir	Human immunodeficiency virus disease without mention of associated disease or condition, clinical stage unspecified	J05AR11
efavirenz + lamivudine + tenofovir	Human immunodeficiency virus disease without mention of associated disease or condition, clinical stage unspecified	
entecavir	Chronic hepatitis B	J05AF10
lopinavir + ritonavir	Human immunodeficiency virus disease without mention of associated disease or condition, clinical stage unspecified	J05AR10
ombitasvir + paritaprevir + ritonavir	Chronic hepatitis C	J05AP53
oseltamivir	Influenza due to identified seasonal influenza virus	J05AH02
ribavirin	Viral haemorrhagic fever, not elsewhere classified Chronic hepatitis C	J05AB04
ritonavir	Human immunodeficiency virus disease without mention of associated disease or condition, clinical stage unspecified	J05AE03
valaciclovir	Zoster Varicella Herpes simplex infections	
zidovudine	Human immunodeficiency virus disease without mention of associated disease or condition, clinical stage unspecified	J05AF01

Dependence (different procurement system, not publicly available)

[5] Only atanazavir is reimbursed.
[6] Fixed dose combination is not reimbursed, but individual medicines are.

buprenorphine	Opioid dependence	
methadone	Opioid dependence	N07BC02
nicotine replacement therapy	Nicotine dependence	N07BA01
varenicline	Nicotine dependence	N07BA03

Tropical diseases (not relevant for Latvia)

amodiaquine	Malaria due to Plasmodium falciparum	P01BA06
amodiaquine + sulfadoxine + pyrimethamine	Malaria	P01BA06, P01BD51
artemether	Malaria due to Plasmodium falciparum	P01BE02
artemether + lumefantrine	Malaria due to Plasmodium falciparum	P01BF01
artesunate	Malaria due to Plasmodium falciparum	P01BE03
artesunate + amodiaquine	Malaria due to Plasmodium falciparum	P01BF03
artesunate + mefloquine	Malaria due to Plasmodium falciparum	P01BF02
artesunate + pyronaridine tetraphosphate	Malaria due to Plasmodium falciparum Malaria due to Plasmodium vivax	P01BF06
benznidazole	Chagas disease	P01CA02
chloroquine	Malaria due to Plasmodium ovale Malaria due to Plasmodium vivax Malaria due to Plasmodium malariae Malaria due to Plasmodium vivax Rheumatoid arthritis	P01BA01
dapsone	Leprosy	J04BA02
deferasirox	Other specified sickle cell disorders or other haemoglobinopathies	
deferoxamine	Other specified sickle cell disorders or other haemoglobinopathies	V03AC01
diethylcarbamazine	Lymphatic filariasis	P02CB02
dihydroartemisinin + piperaquine phosphate	Malaria due to Plasmodium falciparum	P01BF05
diloxanide	Amoebiasis	P01AC01
eflornithine	African trypanosomiasis	P01CX03
fexinidazole	African trypanosomiasis	P01CA03
fexinidazole	African trypanosomiasis	P01CA03
flucytosine	Cryptococcosis	J02AX01
ivermectin	Strongyloidiasis Ascariasis Trichuriasis Hookworm diseases Ancylostomiasis Onchocerciasis Lymphatic filariasis Scabies	P02CF01
mefloquine	Malaria due to Plasmodium falciparum	P01BC02
meglumine antimoniate	Visceral leishmaniasis Mucocutaneous leishmaniasis Cutaneous leishmaniasis	P01CB01
melarsoprol	African trypanosomiasis	P01CD01

miltefosine	Visceral leishmaniasis Mucocutaneous leishmaniasis Cutaneous leishmaniasis	P01CX04
niclosamide	Hymenolepiasis Diphyllobothriasis Taeniasis due to Taenia saginata Taeniasis due to Taenia solium Pellagra	P02DA01
nifurtimox	African trypanosomiasis Chagas disease	P01CC01
oxamniquine	Schistosomiasis due to Schistosoma mansoni	P02BA02
paromomycin	Visceral leishmaniasis	A07AA06
pentamidine	African trypanosomiasis Pneumocystosis	P01CX01
praziquantel	Diphyllobothriasis Taeniasis due to Taenia saginata Taeniasis due to Taenia solium Hymenolepiasis Paragonimiasis Clonorchiasis Opisthorchiasis Schistosomiasis Cysticercosis of central nervous system	P02BA01
primaquine	Malaria due to Plasmodium vivax	P01BA03
proguanil	Malaria due to Plasmodium falciparum	P01BB01
pyrimethamine	Toxoplasmosis	P01BD01
quinine	Malaria due to Plasmodium falciparum	P01BC01
sodium stibogluconate	Cutaneous leishmaniasis	P01CB02
sulfadiazine	Toxoplasmosis	J01EC02
sulfadoxine + pyrimethamine	Malaria due to Plasmodium falciparum	P01BD51
suramin sodium	African trypanosomiasis	P01CX02
griseofulvin	Dermatophytosis	D01BA01
tinidazole	Amoebiasis	
triclabendazole	Paragonimiasis Fascioliasis	P02BX04
voriconazole	Chronic pulmonary aspergillosis	J02AC03

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