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Availability of medicines in Estonia: an analysis of existing barriers and options to address them

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ACRONYMS USED IN THIS DOCUMENT

APME	Association of Pharmaceutical Manufacturers in Estonia
ATC	anatomical therapeutic chemical
CML	chronic myelogenous leukaemia
DDD	defined daily dose
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHIF	Estonian Health Insurance Fund (Eesti Haigekassa)
EMA	European Medicines Agency
EMI-Net	European Medicines Information Network
ERP	external reference pricing
EU	European Union
GDP	gross domestic product
GMP	good manufacturing practices
HTA	health technology assessment
INN	international nonproprietary name
IRP	internal reference pricing
LIS	Drug Procurement Cooperation (Norway)
MoSA	Ministry of Social Affairs
NAO	National Audit Office
NCD	noncommunicable disease
NGO	nongovernmental organization
OECD	Organisation for Economic Co-operation and Development
Patients W.A.I.T.	patients waiting to access innovative therapies
PPP	purchasing power parity
PVA	price-volume agreement
QALY	quality-adjusted life year
SAM	State Agency of Medicines (Ravimiamet)
SPC	summary product characteristics
SSRI	selective serotonin reuptake inhibitor
VAT	value-added tax
WTP	willingness to pay

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The authors thank the Estonian Ministry of Social Affairs, the Estonian Health Insurance Fund and the Estonian State Agency of Medicines for providing data for this study, discussing the opportunities and challenges affecting availability of medicines in Estonia, answering our many follow-up questions and providing feedback on early drafts of this report. We also thank the Association of Pharmaceutical Manufacturers in Estonia and the two representatives of wholesaler companies for meeting us and providing their perspectives on the subjects analysed in this report.

EXECUTIVE SUMMARY

Background and scope of activity

The limited selection of available medicines in Estonia – in terms of different formulations and number of generics on the market in comparison with other European Union (EU) countries – was highlighted both in the draft medicine policy and by the National Audit Office (NAO) in its 2012 audit. As a response to these problems, the former government coalition (April 2014 to March 2015) asked the Ministry of Social Affairs (MoSA) to develop a proposal to improve the situation. The present study aimed to collect and analyse evidence to inform such a proposal.

The study aimed to identify possible barriers to increasing the availability of medicines in Estonia and to suggest options to overcome them. The analysis included a review of relevant national and EU legislation regulating the marketing of pharmaceuticals and local practices relating to pricing, reimbursement and procurement.

Methodology

The study used both qualitative and quantitative methods. Qualitative methods included a review of relevant peer-reviewed and grey literature and a series of face-to-face or electronic meetings with key stakeholders, which were conducted on 19 and 20 February 2015. Quantitative methods included analysis of availability, price and consumption data from the Ministry of Social Affairs, the State Agency of Medicines (SAM) and the Estonian Health Insurance Fund (EHIF).

Results

In 2013, social health insurance contributions, in the form of payroll tax, accounted for 87% of general government expenditure on health. As of December 2014, 94% of the Estonian population was covered and therefore eligible for full or partial reimbursement of outpatient medicines in the “discount list” (list of reimbursed medicines) and of inpatient medicines.

In 2014, the EHIF spent 14% of its budget on compensated medicines in outpatient settings. Out-of-pocket payments on prescription medicines included in the “discount list”, as a proportion of total spending on compensated medicines, have gradually decreased, from 38.0% in 2005 to 31.7% in 2014. Only during the years of the financial crisis was there an increase (38.6% in 2007 and 38.5% in 2008). Patient co-payments are perceived as high in the country and there has therefore been emphasis on trying to reduce them.

In 2013, total expenditure on outpatient medicines and other medical non-durables (US\$ 290 per capita at PPP) was rather contained in Estonia in comparison with other OECD countries (OECD average US\$ 527 per capita at PPP). While public health expenditure as a percentage of total health expenditure was high (77.7% vs OECD average of 72.7%), the absolute total health expenditure was rather low (US\$ 1542 per capita at PPP vs OECD average of US\$ 3453). It should also be noted that, although 18.8% of total health expenditure (both public and private) in Estonia was spent on outpatient medicines and other medical non-durables in 2013 (OECD average 16.7%), health expenditure as a percentage of gross domestic product (GDP) was below the OECD average (6.0% vs OECD average 8.9%).

Most medicines licensed in Estonia as of March 2015 were authorized through the central EU marketing authorization procedure (total number 2092, with different strengths and formulations counting as different marketing authorizations). A further 1494 were authorized through the national procedure, 1377 through the decentralized procedure and 826 through mutual recognition. However, the fact that a medicine is licensed does not mean it is available on the market. For instance, 74% of centrally authorized products (1540) were not sold on the Estonian market in the past three years. This percentage was lower for those authorized through the decentralized procedure (60%, 831) or mutual recognition (37%, 302) and lowest for nationally authorized medicines (10%, 155).

Doctors and professional organizations can make an application to SAM for the use of non-authorized medicines. SAM may grant permission if the case is clinically justified. In 2011, there were almost 8000 such applications, covering 110 different active substances, in 2014 there were about 5000 such applications. Non-registered medicinal products account for 2% of the total market for pharmaceuticals in Estonia.

The NAO report analysed the length of time needed to issue marketing authorizations in 2011 using the decentralized, mutual recognition and national procedures. While the first two of these procedures remained broadly within the prescribed timeframes (apart from the translation of product information), the national procedure took three times as long as prescribed (622 days in 2011 vs 240).

Between January 2013 and May 2015, out of 140 medicines that obtained EU marketing authorization, 40 were the subject of applications for reimbursement in Estonia. For 34 medicines, a reimbursement application was not needed: 19 of these were already on the inpatient service list, 13 were used in national programmes and two were lifestyle medicines and thus not eligible for reimbursement. There were, however, 66 medicines for which no application was made: 41 on-patent medicines (including nine medicines for oncology, seven for diabetes and five for the endocrine system) and 25 generic drugs. Of the 40 applications for reimbursement, 21 have been decided; the remaining are still pending. Four applications have passed the deadline for assessment.

Discussion

While the authorities have made efforts to simplify some processes, many hurdles remain, particularly in the pricing and reimbursement process. We were not provided concrete evidence that anything is being done to address these problems, other than a commitment to train more staff. However, assessment times were shortened between 2011 and 2014, mainly as a result of shorter discussion times in the Committee for Medicinal Products and a shorter time needed to finalize the new directive. The key bottleneck is the assessment by SAM of medical need, availability of alternative treatments, efficacy, safety, utilization of the current product and alternatives in Estonia and other countries, potential for use and misuse, and rational use. The underlying issue appears to be insufficient funding to hire additional staff.

Overall, it seems that a “pull” effect and proactive planning are missing (e.g. how many generics and which products are needed?). Sometimes the “push” comes from doctors; an example is biological treatment of rheumatoid arthritis.

Various steps in the right direction have already been taken, but need to be strengthened. In particular, more dialogue is needed among the different stakeholders, public and private, with an interest in improving access to medicine. The Baltic package, which is in principle a good approach to address the issue of small volumes, has not delivered the expected results. This does not mean that multi-language labelling should not be pursued, but that compromises need to be found to make it work.

Finally, expectations of what can be achieved at current spending levels need to be realistic. Estonia spent only 5.7% of its GDP on health in 2014 (EU average 10.1%), and although the country’s economy has grown rapidly in the past 15 years, the GDP per capita in 2014 was still below the EU average (US\$ 25 865 vs US\$ 34 653 GDP at PPP, constant 2011); this means that Estonia is spending substantially less on health than the EU average.

Limitations

This assessment was based on a 2-day mission in Tallinn, Estonia, with subsequent data analysis and follow-up with competent authorities. A key limitation of the study relates to the analysis of availability of medicines. Ideally, this should have been conducted on the basis of international non-proprietary name (INN), rather than brand–strength–formulation. However, at the time of the analysis, these were the only data available. It was recognized during the interviews that it is not clear whether there is an unmet therapeutic need as a result of non-entry or delayed entry of new medicines. As is currently widely debated in the literature, many new medicines are “me-too” products, with little added therapeutic value. It would be important to conduct a

study to link availability to indicators of therapeutic value, to gauge whether an actual medical need gap exists in some therapeutic areas. Another limitation of this study is that we were not able to meet with the association of pharmacists, so could not include their views in our assessment. Further, time constraints meant that we could meet with only one large and one small wholesaler.

Recommendations

A common vision and roadmap

- Resume the national multistakeholder policy dialogue started in 2012–13, which included the MoSA, the EHIF, SAM, the APME, and other relevant stakeholders, to define areas of work to improve access to medicines. Include this in the national medicines policy.
- Within the policy dialogue, set up working groups to take specific issues forward.
- The updating of the national medicines policy offers an ideal opportunity to develop a common vision and a road map linked with specific objectives, concrete actions, targets, and a monitoring plan, with clear lines of accountability.
- Establish a multistakeholder mechanism to oversee the implementation of the medicines policy and provide a platform for regular discussion of issues related to medicines.
- Establish which medicines are needed to address the main public health needs of Estonia, including both on-patent and off-patent medicines and work with other stakeholders in the multistakeholder dialogue towards increasing their availability
- Evidence is needed to inform decision-making and action, for example, studies on prescribing practices particularly for patients with multiple morbidities moving across different levels of care, determinants of generic penetration across different disease areas and whether non-entry or delayed entry of new medicines is causing an avoidable therapeutic gap should be conducted for selected therapeutic areas.
- Proactively invite manufacturers to make a submission for reimbursement of medicines considered of high public health importance. Take measures (including providing increased funding for staff) to ensure that assessment times are within those prescribed by the EU Transparency Directive.

Sharing experiences

- Enhance experience-sharing and increase collaboration with other Baltic countries in areas relevant to availability of medicines (in particular in the areas of market entry, generic competition and strategic procurement); consider similar collaboration with the Nordic countries.
- Expand collaboration with other countries in the area of health technology assessment (HTA) and use of medicines using existing networks (e.g. EUnetHTA, advance-HTA, Piperska).

Addressing procedural barriers

- Explore options to further reduce the time needed for assessment by SAM, the discussions of the Committee for Medicinal Products and the finalization of the Ministerial directive.
- Consider allowing manufacturers to bid as well as wholesalers
- Conduct regular procurement reviews (e.g. ABC analysis) and use the findings to improve procurement practices and generate efficiencies through improved bidding environment
- Discuss with hospital managers and doctors their concerns relating to implementation of joint calls for tender for medicines. Use evidence from other countries to demonstrate the benefits that are likely to accrue for the patients and the health care system. (The Norwegian hospital procurement system, drug procurement cooperation (LIS), is a good example (1).)
- If a medicine deemed important to address the health needs of a sizeable group Estonian patients does not have an EU-wide marketing authorization, proactively seek approval through the decentralized or mutual recognition procedure, which have been shown to be the fastest channels. For small groups of patients it may be less individual patient request may be a better solution.

Promoting use of generics and biosimilars

- Introduce mandatory generic substitution at pharmacy level.
- Continue the campaigns to raise patients' awareness about generics and INN prescribing. Include also information on biosimilars.

Quality use of medicines¹

- Identify suitable indicators and conduct prescribing audits using data from the e-prescribing system to incentivise evidence-based prescribing by providing feedback to physicians
- Identify what the role of different actors in health sector should be in coordinating pharmaceutical care of patients with multiple morbidities
- Strengthen collaboration between the doctor and the pharmacist in delivering high quality pharmaceutical care and promoting quality use of medicines

Orphan medicines

Discuss the feasibility of implementing existing proposals to increase availability of orphan medicines, including the increased use of individual patient funding requests, HTA and labelling requirements within the multistakeholder dialogue.

Evidence for decision-making

- Leverage on the wealth of high quality data available – possibly in collaboration with the University of Tartu - on use of medicines to conduct analysis to drive policy action and improve pharmaceutical care.

Long-term vision

- Strengthen the use of horizon scanning and targeted proactive planning of pharmacotherapeutic needs.

Increase expenditure on health and medicines in order to increase access to new medicines. Avoid jeopardizing adequate salaries for hospital health professionals in favour of procurement of hospital medicines.

¹ The scope of this report was to review availability of medicines and the methodology did not seek to specifically address issues related to quality use of medicines. Nevertheless, making cost-effective medicines available without improving the quality of their use is not going to reach one of the three key goals of a health system- as defined by WHO Health System Performance Framework- which is to improve health outcomes for the population it serves.

BACKGROUND

The limited selection of available medicines in Estonia – in terms of different formulations and number of generics on the market in comparison with other European Union (EU) countries – was highlighted in the draft medicine policy (2). The problem was also highlighted by the Estonian National Audit Office (NAO) in their 2012 audit, which provided evidence of several underlying issues (3). One specific issue is the limited interest of pharmaceutical manufacturers in marketing their products in Estonia. A recommendation has therefore been made to make the market more attractive to manufacturers and to send a strong message that the state is interested in them. Another issue raised by the NAO was the length of the national marketing authorization, pricing and reimbursement processes. As a response to these problems, the former government coalition (April 2014 to March 2015) asked the Ministry of Social Affairs (MoSA) to develop a proposal to improve the situation. The present study aimed to collect and analyse evidence to inform such a proposal.

SCOPE OF ACTIVITY

This study aimed to identify possible barriers to increasing the availability of medicines in Estonia and to suggest options to overcome them. The analysis included a review of relevant national and EU legislation regulating the marketing of pharmaceuticals, and local practices relating to pricing, reimbursement and procurement.

The specific objectives of the study were:

1. to review features of the Estonian health system and pharmaceutical market relevant to access to medicines;
2. to look for evidence of non-availability of medicines due to lack of marketing authorization, decisions of manufacturers not to market, and shortages;
3. to explore possible barriers and disincentives to applications for marketing authorization and to the subsequent marketing of authorized products in Estonia;
4. to identify possible solutions and best practices to improve the availability of medicines in Estonia, drawing from other countries' experiences.

METHODOLOGY

The study used both qualitative and quantitative methods. Qualitative methods included a review of relevant peer-reviewed and grey literature and a series of face-to-face or electronic meetings with key stakeholders, which were conducted on 19 and 20 February 2015.² Quantitative methods included analysis of availability, price and consumption data from the Ministry of Social Affairs, the State Agency of Medicines (SAM) and the Estonian Health Insurance Fund (EHIF). The study used a variety of data sources, which are clearly indicated throughout the report.

² The mission agenda, with the names of the stakeholders met, is given in Annex 1.

OVERVIEW OF THE HEALTH SYSTEM AND PHARMACEUTICAL MARKET

Estonia has a population of 1.3 million people (January 2015) and a life expectancy at birth of 72.3 years for males and 81.5 years for females in 2014 (4). Noncommunicable diseases (NCDs) are estimated to account for 93% of all deaths, of which 55% are due to cardiovascular diseases, 24% to cancer, 2% to chronic respiratory diseases, 1% to diabetes and 11% to other NCDs. The remaining deaths are due to injuries (5%) and communicable, maternal, perinatal and nutritional conditions (2%) (5). The much higher mortality from cardiovascular conditions and cancer in men than in women is likely to be an important determinant of the almost 10-year gap in life expectancy. There has been a steep decline in mortality from cardiovascular diseases in both men and women since 2000, but hardly any change in cancer mortality over the same period (5).

Stakeholders

Ministry of Social Affairs

MoSA was created in 1993 by merging the Ministry of Health, the Ministry of Social Welfare and the Ministry of Labour (6). The Ministry's main responsibilities in the area of health are health policy formulation, monitoring of population health and organization of the national health system (6).

Estonian Health Insurance Fund

EHIF is the result of a merger in 2001 of the Central Sickness Fund and the 17 regional sickness funds. Its responsibilities include the financing of health care, by covering the costs of various health services, financing of the purchase of medicinal products and medical devices, contracting of health service providers, paying for temporary sick leave and maternity leave, and organization and support of quality in health care (e.g. development of clinical guidelines).

State Agency of Medicines

SAM is the national drug regulatory authority for human and veterinary medicinal products in Estonia and was created in 1991 (7). The Agency seeks to ensure: that medicinal products authorized for use in Estonia in the prevention, treatment and diagnosis of human and animal diseases are effective, safe and of high quality; that medicinal products are used for their intended purpose; and that the safety and protection of rights of participants in any clinical trials of medicinal products conducted in Estonia are guaranteed (8).

Patient representatives

Patient organizations see their role as managing complaints from patients. In general, nongovernmental organizations (NGOs) in Estonia have limited experience of participating in political discussions and their contribution is therefore not as significant as in some other EU countries with a longer tradition of NGO work. This is largely for historical reasons, a legacy of Soviet times when civil society initiatives were not encouraged. It seems that diabetes and multiple sclerosis patients are collectively active but not, for example, rheumatoid arthritis patients.

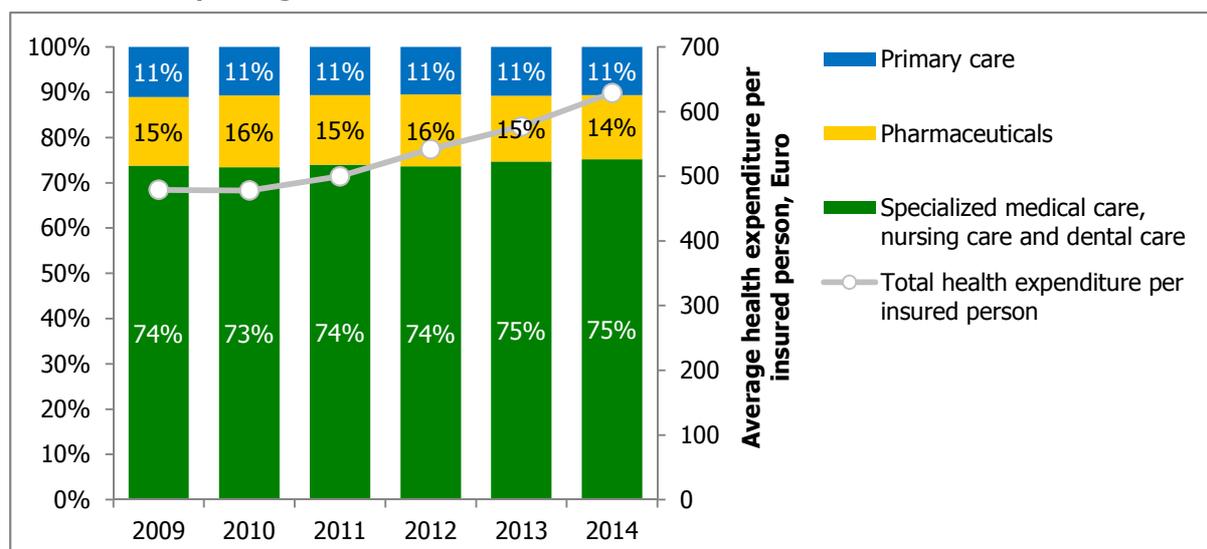
Financing and expenditure on medicines

In 2013, social health insurance contributions, in the form of payroll tax, accounted for 87% of general government expenditure on health (9). As of December 2014, 94% of the Estonian

population was covered³ and therefore eligible for full or partial reimbursement of outpatient medicines in the “discount list” (list of reimbursed medicines) and of inpatient medicines.

In 2014, the EHIF spent 14% of its budget on compensated medicines in outpatient settings (Figure 1). Out-of-pocket payments on prescription medicines included in the “discount list”, as a proportion of total spending on compensated medicines, have gradually decreased, from 38.0% in 2005 to 31.7% in 2014 (10, 11). Only during the years of the financial crisis was there an increase (38.6% in 2007 and 38.5% in 2008).

Figure 1. Total health expenditure per insured person (euros) and distribution of health spending^a



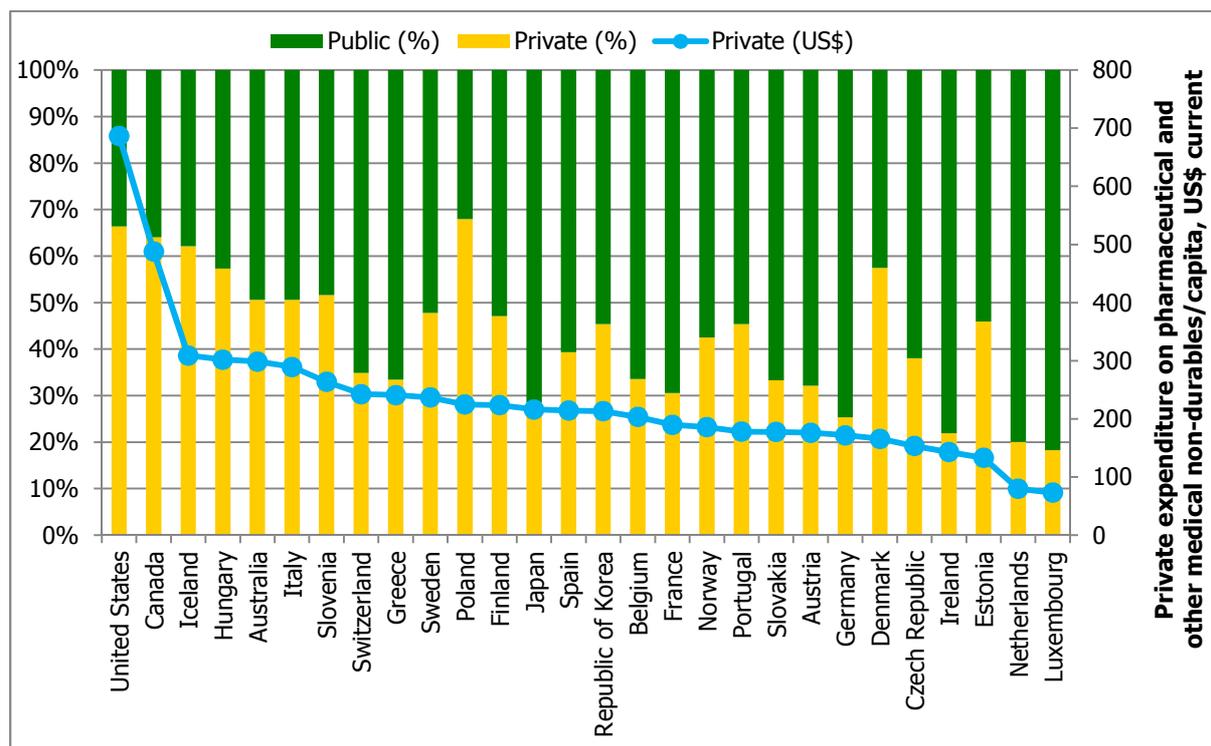
^a Expenditure on inpatient medicines is included in expenditure on specialized care.
 Source of data: EHIF (11).

Patient co-payments are perceived as high in the country and there has therefore been emphasis on trying to reduce them. While private expenditure on outpatient medicines as a percentage of total pharmaceutical expenditure is high (46% in 2013), in absolute terms it was among the lowest (US\$ 133 at PPP in 2013) in comparison with other OECD countries (Figure 2).

Total expenditure on outpatient medicines and other medical durables (US\$ 290 per capita) is rather contained in Estonia in comparison with other OECD countries (Figure 3).

³ Authors’ calculation based on number of insured people (10) as of 31 December 2014 divided by the resident population as of 1 January 2015 (3).

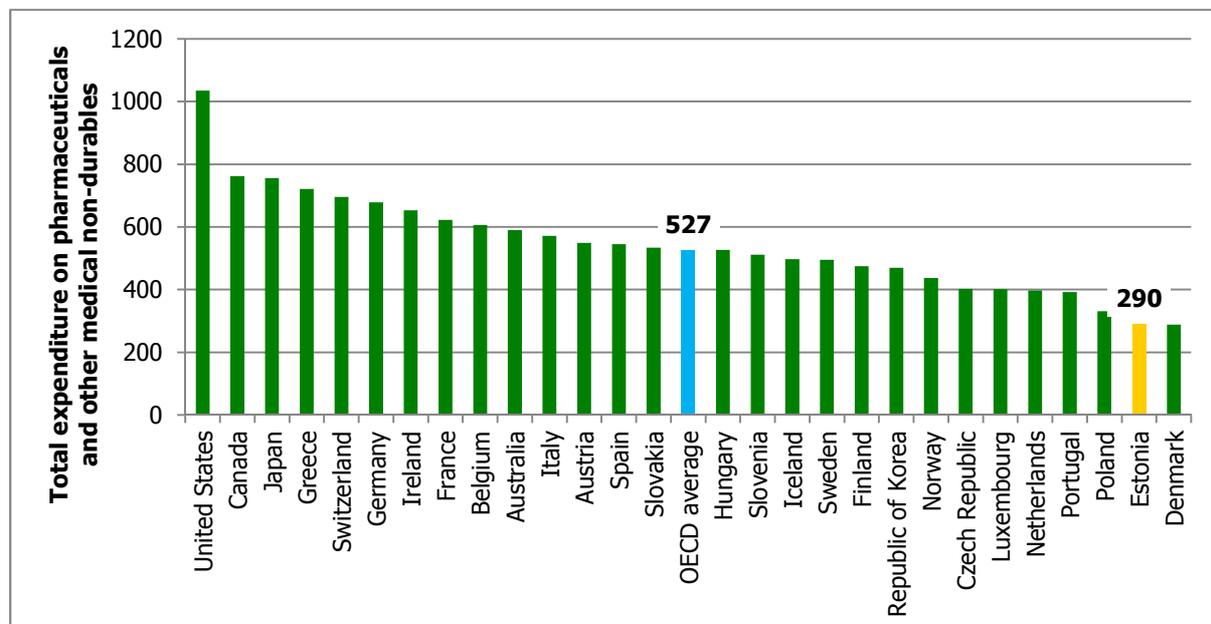
Figure 2: Public and private expenditure on medicines and other medical durables in OECD countries in 2013^a



^a This figure does not include data on medicines dispensed in hospitals (both day-units and inpatient). Data for Australia, Ireland, Japan, and Luxembourg are for 2012; data for Israel are for 2011. Countries with data older than were 2010 excluded.

Source: (12)

Figure 3. Total per capita expenditure on pharmaceuticals and other medical non-durables in current US dollars at purchasing power parity in 2013^a

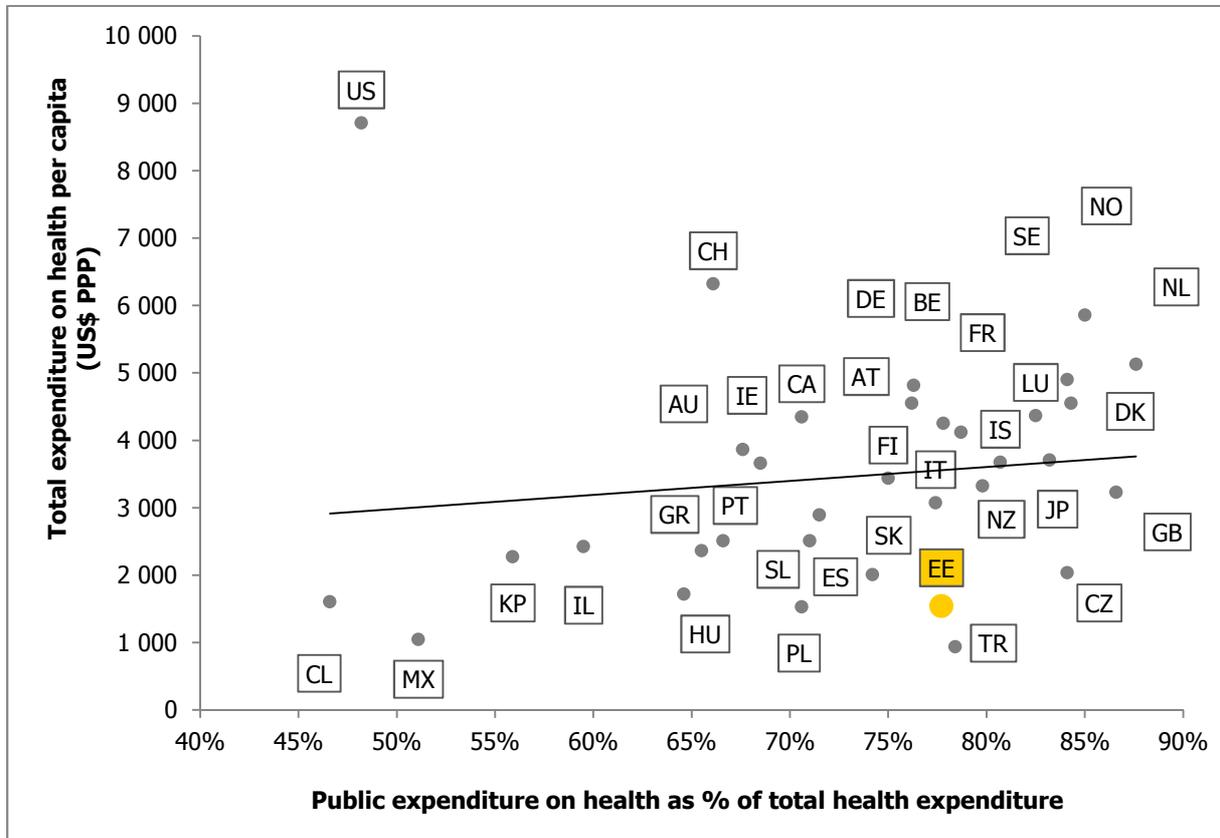


^a This figure does not include data on medicines dispensed in hospitals (day units and inpatient). Data for Australia, Ireland, Japan, and Luxembourg are for 2012; data for Israel are for 2011. Countries with data older than were 2010 excluded.

Source: (12).

While public health expenditure as a percentage of total health expenditure is high (78%), the absolute total health expenditure is low (US\$ 1542 at PPP) in comparison to other OECD countries (Figure 4).

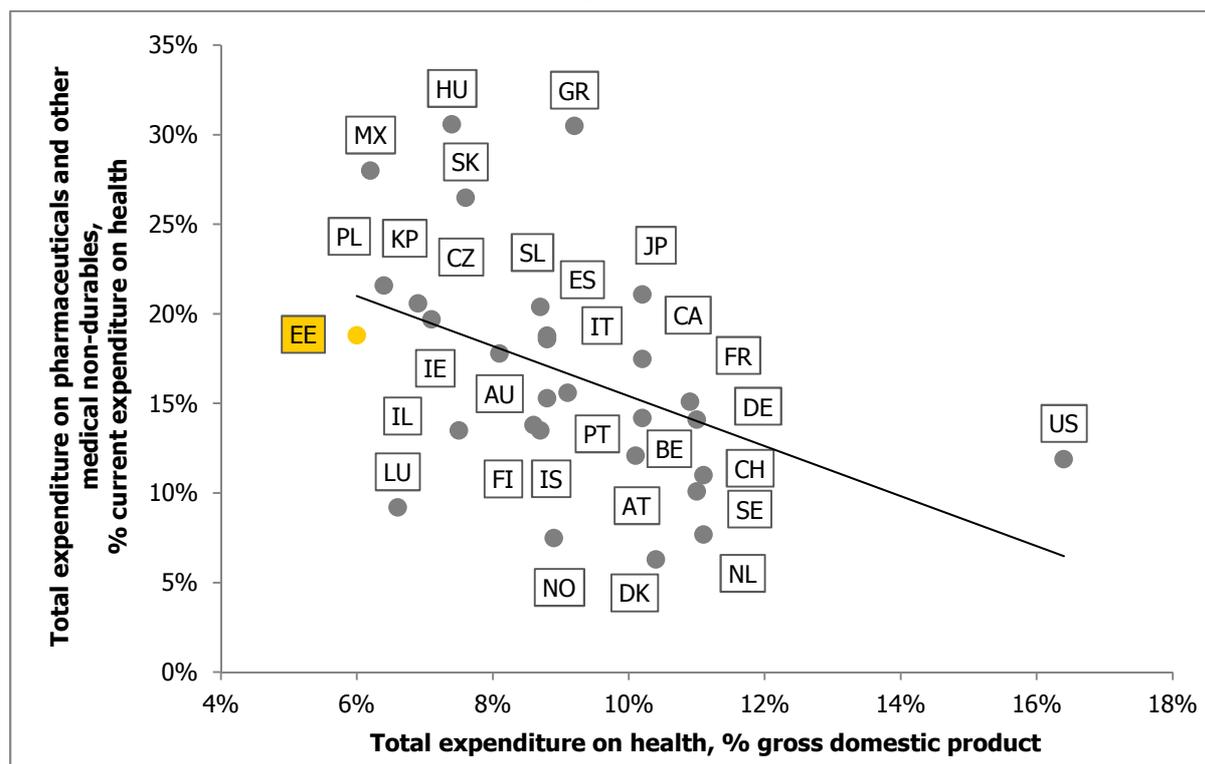
Figure 4. Total health expenditure per capita (current US\$ PPP) against percentage public health expenditure in 2013, OECD countries^a



^a This figure does not include data on medicines dispensed in hospitals (day units and inpatient). Data for Australia, Ireland, Japan, and Luxembourg are for 2012; data for Israel are for 2011. Countries with data older than were 2010 excluded. Source: (12).

It should also be noted that, although 18.8% of total health expenditure (both public and private) in Estonia was spent on outpatient medicines in 2013, health expenditure as a percentage of gross domestic product (GDP) was rather low (5.9%) in comparison with other OECD countries (Figure 5).

Figure 5. Pharmaceutical expenditure as a percentage of total health expenditure against total health expenditure as a percentage of GDP in 2013^a



^a This figure does not include data on medicines dispensed in hospitals (day units and inpatient). Data for Australia, Ireland, Japan, and Luxembourg are for 2012; data for Israel are for 2011. Countries with data older than were 2010 excluded. Source: (12)

Production, distribution and sales of medicines

Local manufacturing capacity

There are no researching pharmaceutical companies manufacturing in Estonia, and there are only two local generic-manufacturing companies.

Wholesalers

There were 51 wholesalers of human and veterinary products in 2015 in Estonia, one more than in 2014 (Table 1).

Table 1. Number of wholesalers of human and veterinary medicinal products in Estonia, 2011–2015

	2011	2012	2013	2014	2015
Wholesalers of human and veterinary medicines	46	50	53	50	51
Wholesalers of veterinary medicines only	7	5	5	6	6
Total	53	55	58	56	57

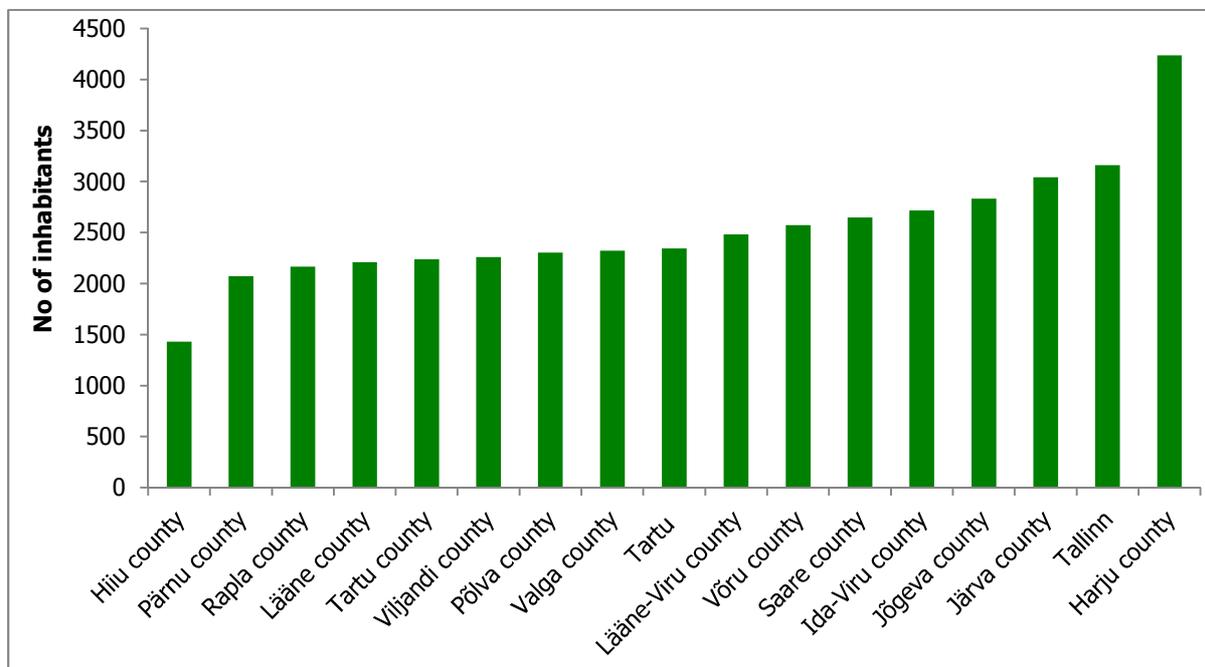
Source: (13).

In 2014, more than 75% of the market was concentrated among three large wholesalers: Magnum Medical (29.6%), Tamro Estonia (25.6%), and Apteekide Koostöö Wholesale (21.2%). The remaining market share was divided among the Estonian Health Board (4.9%), Baltfarma (4.2%), Roche Estonia (4.0%), Oriola (3.0%) and other wholesalers, each with a market share under 2% (13).

Pharmacies

There were 476 pharmacies (including branches) in Estonia as of 1 January 2015. The average number of retail pharmacies on 1 January 2014 was 1 per 2753 inhabitants (Figure 6).

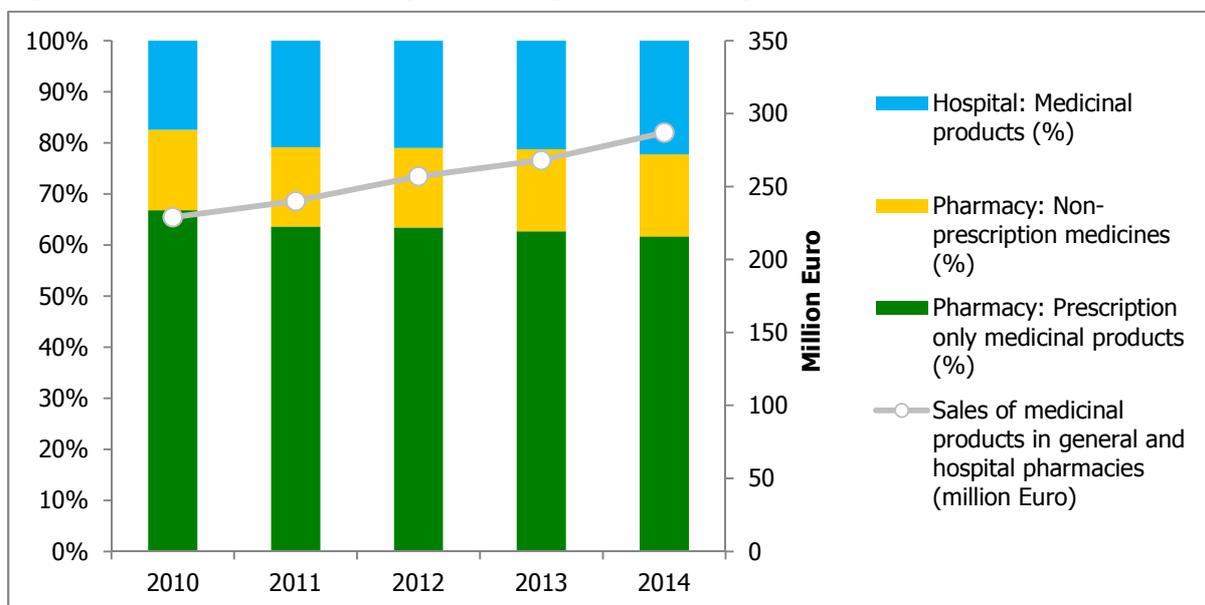
Figure 6. Number of inhabitants per pharmacy in major cities and counties in Estonia, 1 January 2014



Source: based on data from (14) and (14), calculation by the authors.

In 2014, prescription-only retail medicines made up 63% of the pharmaceutical market value, hospital medicines 21%, and non-prescription retail medicines 16% (Figure 7).

Figure 7. Sales of medicinal products in general and hospital pharmacies



Source: (15).

On 20 March 2015, the changes in the Medicinal Products Act of Estonia entered into force (16). The main reform concerned ownership of pharmacies. By April 2020, wholesalers will no longer be allowed to own pharmacies and 50% of each pharmacy has to belong to the pharmacist holding the general

pharmacy activity licence. The named pharmacist must work as manager in at least one general pharmacy operating on the basis of an activity licence issued under her or his name.

Pricing and reimbursement

Pricing in the on-patent market

External reference pricing (ERP) is conducted using prices from Latvia, Lithuania and Slovakia⁴ and an annual re-pricing system is in place. Internal reference pricing (IRP) is also used if applicable. In such cases, the price of a new medicine is compared with prices of other therapeutically similar medicines that are marketed and reimbursed in Estonia.

The basis for pricing negotiations with manufacturers is carriage- and insurance-paid (CIP) prices in other countries, cost-effectiveness and budget impact analysis. Given that prices in the reference countries are quite uniform, the main leverage elements are the results of the pharmacoeconomic analysis. This may lead to negotiation of a different price than the one submitted in the reimbursement application.

The MoSA can secure price and volume for one year, through negotiation of price–volume agreements (PVAs), in which the volume expected to be needed for one year is predicted. At the end of the year, the actual volume consumed is reviewed and, if necessary, the agreed volume for the next year increased; the price will usually decrease. Exceeding the predicted volume does not automatically stop reimbursement. PVAs are used when there is only one version of a product on the market, which generally applies to on-patent products but can sometimes apply to the off-patent market. Overall, use of PVAs in the generic market is limited.

In addition, risk-sharing agreements are used; examples of such agreements are telaprevir for treatment of hepatitis C, brentuximab for lymphoma and mifamurtide for osteosarcoma.

Pricing in the off-patent market

The first generic medicine to enter the market has to be at least 30% cheaper than the original brand. Once this reference price is set, each new medicine with the same international non-proprietary name (INN) has to be priced at least 10% lower than the lowest-priced product, with the same ATC-5 group, on the market. Internal reference pricing is used for all reimbursed medicines containing the same active substance and with the same route of administration (17). Reference prices are established and updated on a quarterly basis, and there are specified conditions for updating them (17). The second-lowest price in the group is set as the reimbursement price. Therapeutic clustering may also be used but there is no legislative support so this depends on negotiation. Currently, it is used for diabetes.

Reimbursement in the outpatient sector

There are four reimbursement rates (called “discount” in Estonia): 100%, 90%, 75% and 50%. All these reimbursement groups are subject to a fixed patient co-payment (€1.27 for the 100%, 90% and 75% groups and €3.19 for the 50% group) and a percentage co-payment of 0%, 10%, 25% and 50%, respectively, of the remaining amount of the reference price or price agreement. If the price of the medicine is higher than the reimbursement price or price agreement, the patient has to pay the excess in addition to any co-payment. Children under 4 years of age benefit from 100% compensation on all medicines included in the list. Children between 4 and 16 years, disabled persons, insured persons over the age of 63 and pensioners benefit from a 90% reimbursement rate for all medicines (18).

⁴ The price cannot be higher than the highest price in the reference countries.

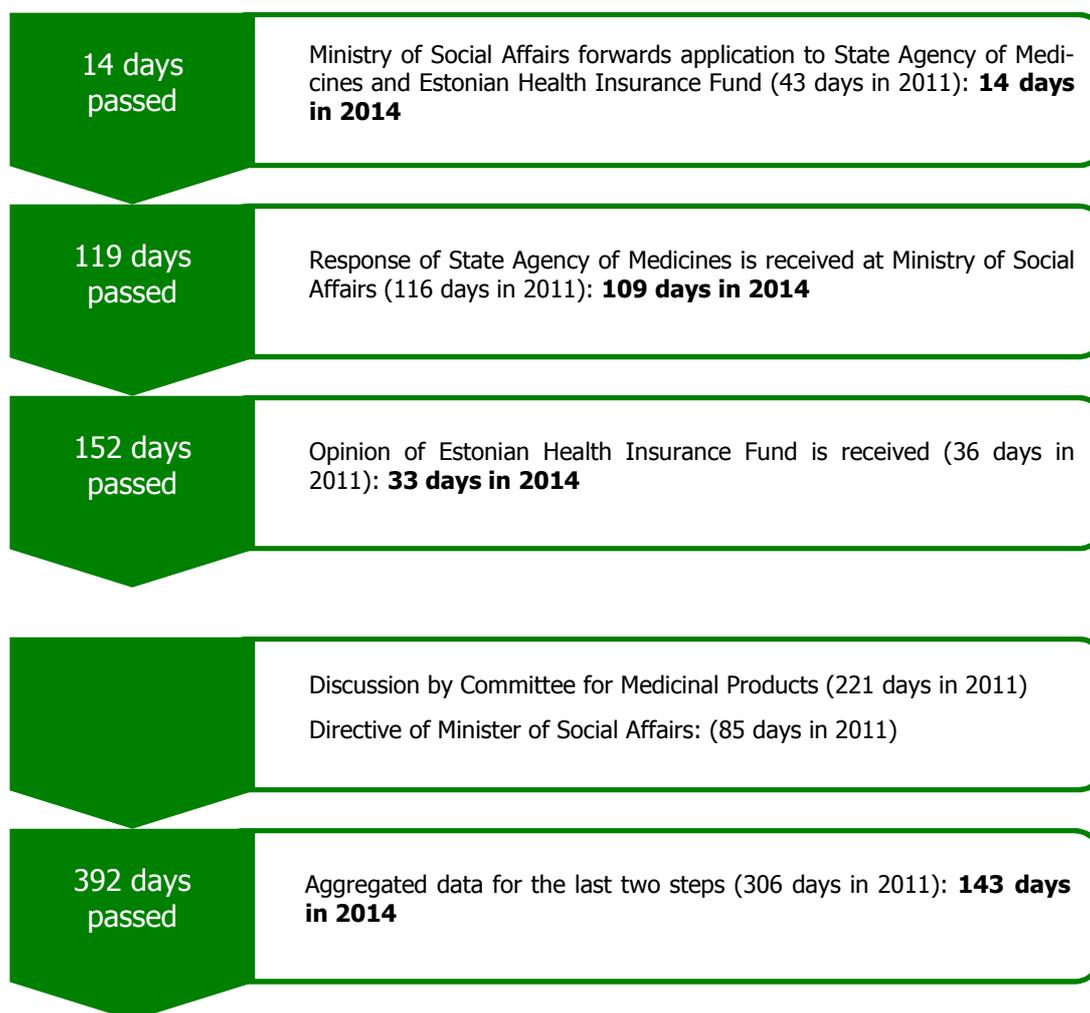
The assessment process for inclusion in the reimbursement list starts with submission to the MoSA of a reimbursement dossier by the local representative of the holder of the marketing authorization. The MoSA then sends the dossier for review to SAM, which makes a recommendation based on medical need, availability of alternative treatments, efficacy, safety, use of the current product and alternatives in Estonia and other countries, potential for use and misuse, and rational use (19). Once SAM's review is completed, the EHIF assesses the cost-effectiveness and budget impact, and whether there is a need to establish reimbursement criteria to ensure rational use of the medicine. A willingness to pay (WTP) threshold of three times the GDP per quality-adjusted life year (QALY) applies; other criteria are also taken into account in the decision-making process. In practice, prices above three times the GDP threshold are generally not reimbursed; however, lower prices are not necessarily reimbursed if other criteria are not met. Cost-effectiveness is the determinant factor, but budgetary considerations also play a role (even though the annual budget for medicines is not fixed). Some positive reimbursement decisions for medicines well above the three times GDP threshold have been made; for example, orphan medicines for Gaucher disease and Fabry disease, costing on average €200 000 a year, were included in the inpatient service list.

If full coverage of the licensed indication is found not to be cost-effective, the EHIF can approve medicines for selected subgroups of eligible patients only. However, it is difficult for EHIF to assess to what extent such prescribing restrictions are respected. Periodic checks of physicians' diagnosis and prescription practices are conducted, and if evidence is found of prescriptions claimed outside the specified indications, the physician may have to pay compensation.

Following the assessment by the EHIF, the Committee for Medicinal Products reviews the evidence and the recommendations of SAM and EHIF and produces its own recommendation for the Minister of Health and Labour, who takes the final decision on whether or not to include the medicine in the list of reimbursed ambulatory medicines.

Figure 8 shows the average time from submission of an application for reimbursement to decision, based on all medicines that got to the decision stage in 2011 and 2014. The overall time was reduced from 501 days in 2011 to 392 days in 2014. This reduction was largely achieved through reductions in the time needed for discussion by the Committee for Medicinal Products and the time to finalize the new directive. The relative contribution of each is unknown, as data were provided in aggregate format.

Figure 8. Average time from submission of an application for reimbursement to decision in 2011 and 2014^a



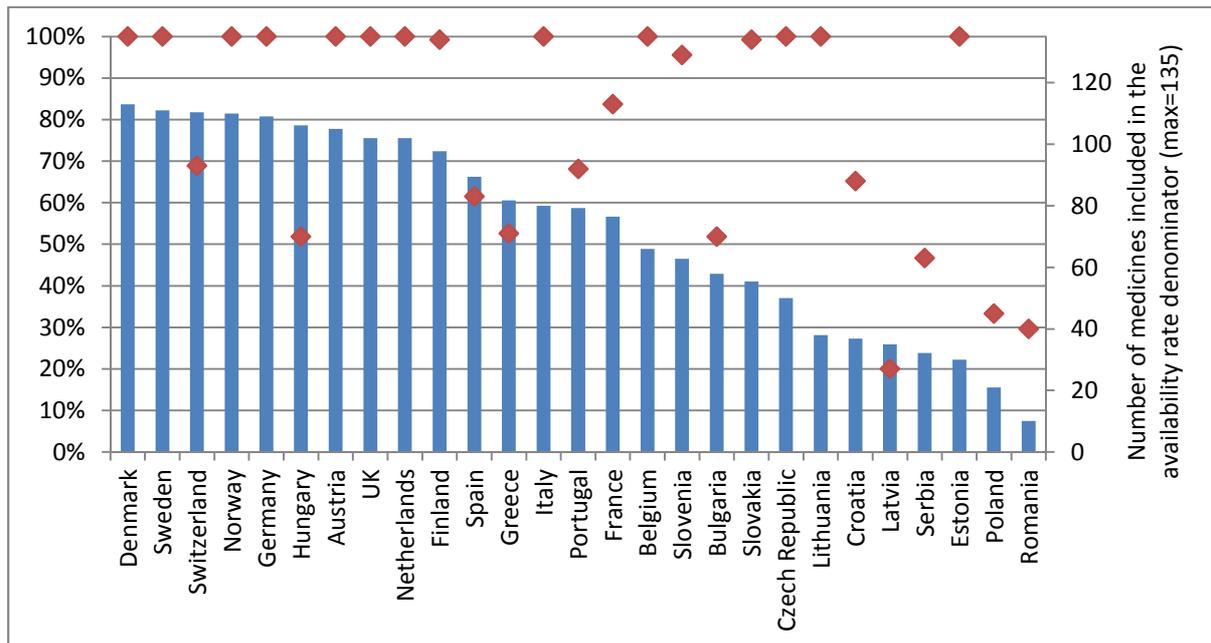
^a For 2014, the first steps include only applications submitted to the MoSA in 2014, of which 5 have been finalized with the ministerial decision. The overall time of 392 days takes into account all applications finalized in 2014. Counts do not include days elapsed during a pause in the assessment process for reasons not dependent on the Estonian authorities (e.g. when the EHIF asks for additional materials from the applicant). Data for 2011 include 30 medicines for which a decision was made in 2011; 21 of these decisions were positive.

Source: data of MoSA, 2011 analysis by NAO (3), 2014 analysis by MoSA.

The European Federation of Pharmaceutical Industries and Associations (EFPIA) estimates an indicator, "Patients W.A.I.T." (patients waiting to access innovative therapies). W.A.I.T. shows, for new medicines, the rate of availability, measured by the number of medicines available to patients in European countries, and the average time between marketing authorization and patient access, measured as the number of days elapsing from the date of EU marketing authorization to the day of completion of post-marketing authorization administrative processes (20).

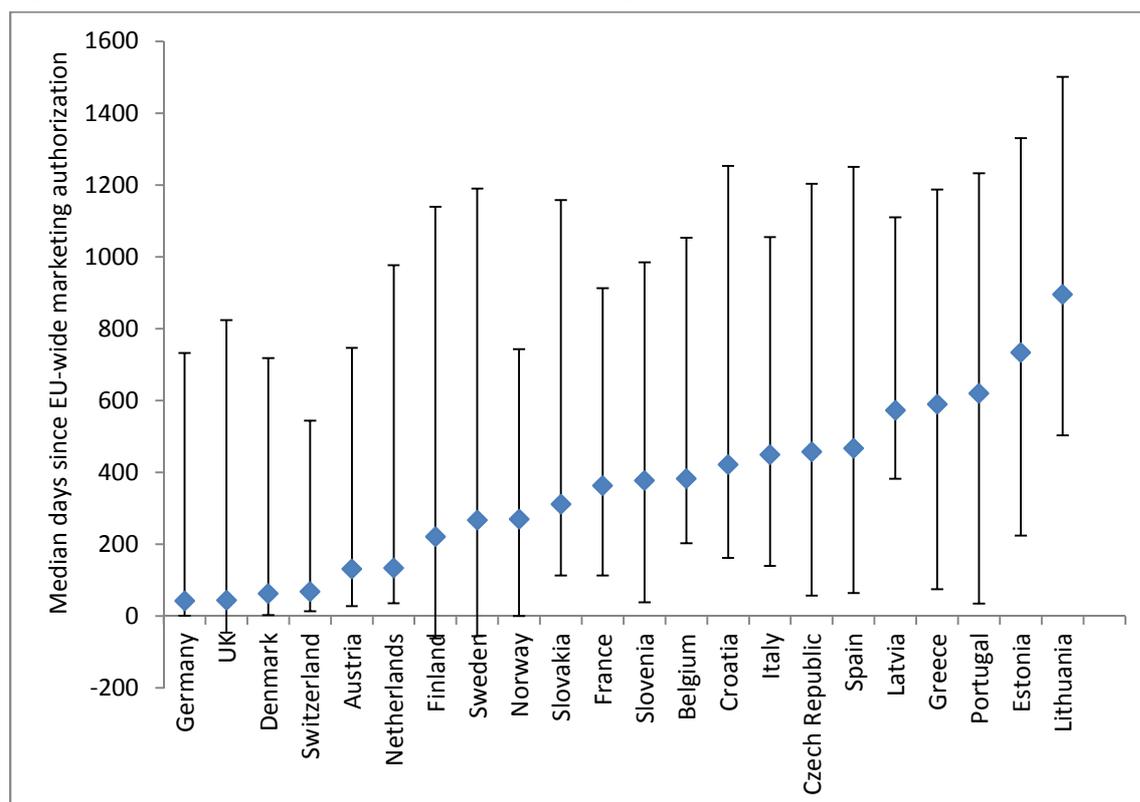
Data are collected on medicines with an EU marketing authorization for an active substance that was not previously authorized in the EU and for which prior marketing authorization outside the EU dates back no more than 10 years. For the period 2011–2014, 135 medicines met these criteria (20), of these, 30 were available in Estonia as of April 2015 (Figure 9).

Figure 9. Availability of innovative medicines in different European countries (100% = maximum 135)^a



^a Data were updated in April or May 2011, except for France and Switzerland (May 2010).
 Source of data: (20).

Lack of completion of post-marketing authorization processes depends on one hand on the speed of these processes but most importantly on whether, and if yes, when, the manufacturer submits the necessary dossiers to apply for pricing and reimbursement. An analysis of submissions of medicines (140 in total), which obtained EU-wide marketing authorization between January 2013 and May 2015, found that –among eligible medicines for reimbursement (106 in total)– there were 66 cases of non-submission for reimbursement in Estonia (MoSA, unpublished observations).

Figure 10: Median time to complete post-marketing processes^a

^a Data on the number of days required to complete post-marketing processes were mostly available only for a subsample of all the medicines included in the availability rate analysis. In the case of Estonia, information was available for 28 medicines.

Note: In some countries pricing and reimbursement can be completed and/or use may start before marketing authorisation is granted, hence the negative median times

Transparency

The first steps have been taken towards increased transparency. For example, during the annual process of updating the inpatient health service list, all submissions and expert opinions on medical issues, cost-effectiveness and budget impact are published on the EHIF website. The meeting minutes of the Committee for Medicinal Products regarding the evaluation of ambulatory medicines are also published. The EHIF also supports the publication of submissions and expert opinion documents for ambulatory medicines in the near future (with protection of confidential information).

Tenders

Each hospital continues to do its own calls for tender, despite encouragement by the EHIF to create greater bargaining power by merging orders. Only a few products are put out to tender centrally. These include vaccines that are part of the national immunization schedule, medicines against tuberculosis and HIV/AIDS (handled by MoSA), methadone (handled by the National Institute of Health Development) and antidotes (handled by the Health Board). Apart from the last-mentioned, no tenders are sought for outpatient medicines.

The law on procurement is generic and not specific to medicines or health products. There is a €27 000 threshold for public procurement before an EU tender is required. Tenders are awarded on the basis of price alone, usually for a one-year period.

Only entities with a wholesaler licence can bid; there are only three large wholesalers, which substantially limits the number of bidders. Wholesalers, and manufacturers with a wholesaler licence (e.g. Roche), have contracts with producers that have offices in Estonia. Wholesalers do not first buy

and then try to find a buyer. A large wholesaler interviewed thought that manufacturers should be allowed to bid and then choose a wholesaler for distribution.

According to the small wholesaler interviewed, the hospital sector has a preference for brand-name medicines, rather than generics. This is because the manufacturers of the original brand medicine will have already been dealing with hospitals for a long time when the generic form enters the market, and they have better skills in dealing with hospitals. However, hospital tender departments are becoming more proactive and have started to challenge doctors who request non-generic drugs without a medical reason. When challenged whether wholesalers may have an incentive to propose the highest-priced product in the tender document, the reply was that this would only be the case if the wholesaler is sure that the hospital will not go to another wholesaler that can offer them a lower price. Also mentioned were the very general nature of the calls to tender and the not always accurate estimation of need.

Clinical guidelines

Several national clinical guidelines were developed by professional bodies between 2003 and 2009. However, there was no standard approach, even though guidance had been developed by EHIF; this resulted in a variety of formats for the guidelines. In 2011, the Estonian handbook for guidelines development was published (21). This was a collaborative process between WHO, Tartu University and the EHIF. Since 2012, national guidelines are developed using a unified process and methodology and are endorsed by the Guideline Advisory Board. However, speciality associations and health care institutions may still develop guidelines for their own use without following the handbook.

As of May 2015, 37 clinical guidelines had been approved by the Guideline Advisory Board and a further seven were in development. Ten had been developed or were being developed using the standard handbook; 32 had been developed before 2011 (22) and were in need of updating. For example, the guideline on general principles of treatment for glaucoma was approved in 2003 and needs to be updated (23). Apart from an outdated guideline on cancer pain management dating from 2003 (24), there are no national guidelines on cancer treatment. Cancer is not the only therapeutic area where clinical guidelines are not available. According to the MoSA, priority is given to the development of clinical guidelines in areas where integrated care plays an important role in the country, e.g. type 2 diabetes. The full list of assessment criteria against which the Guideline Advisory Board evaluates proposals for guidelines is provided in the standard handbook. Where national clinical guidelines are not available, international ones are followed, e.g. the *European Society for Medical Oncology* (25) or the *National Comprehensive Cancer Network* clinical guidelines for cancer (26). As it is quite common for Estonian specialists to be involved in the development and updating of international guidelines, the MoSA finds that there is no need to have Estonian guidelines in every therapeutic area.

However, another stakeholder mentioned that, while clinicians claim to use international guidelines, there is wide variability in treatment. Factors likely to play a role in the implementation of clinical guidelines include the availability of resources – personnel, finance and equipment – which varies across hospitals and the interpretation of recommendations, which can vary even within hospitals. Also, different international recommendations may be used within a therapeutic area. It remains to be verified whether the lack of guidelines in the local language may be an issue for some clinicians.

While it is difficult to assess the actual impact of a lack of standardized clinical guidelines on manufacturers' willingness to launch new medicines and generics in Estonia, it is probably fair to say that unclear treatment pathways are likely to foster uncertainty among manufacturers planning to launch their products in the country.

Barriers to availability of medicines

A 2008 report by the Task Force of the Heads of Medicines Agencies on the availability of human medicinal products in the European Economic Area, chaired by Estonia, highlighted three barriers to availability: 1) the medicine is not registered in the country, 2) the medicine is registered but not marketed, and 3) there is a shortage of a registered medicine on the market (27).

Before a medicine can even enter the health care system, it has to be deemed safe and effective by the competent authority. Following clinical trials to generate evidence on safety and efficacy of new medicines, manufacturers therefore need to seek a licence in order to market their products. In the EU and the European Economic Area (EEA) countries Iceland, Liechtenstein and Norway, in addition to the national procedure, medicines can be authorized through the centralized procedure. The centralized procedure may result in European Commission granting a single marketing authorization valid in all EEA countries mentioned (28). The centralized procedure is compulsory for certain groups of medicines, including those for treating HIV/AIDS, cancer, diabetes, neurodegenerative diseases, autoimmune and other immune dysfunctions, and viral diseases, those derived from biotechnology processes (e.g. genetic engineering), advanced-therapy medicines (e.g. gene-therapy, somatic cell-therapy or tissue-engineered medicines) and officially designated "orphan medicines" (28). For medicines that do not fall into these groups, manufacturers have the option of applying centrally, for medicines of great public health importance, or to the national medicines agencies of the countries of interest.

There are two additional routes for simultaneous authorization in more than one Member State of the EEA. The decentralized procedure allows manufacturers to apply for simultaneous authorization of a medicine in more than one EU country; and the mutual recognition procedure enables manufacturers whose medicine is authorized in one EU Member State to apply for this authorization to be recognized in other EU countries (28).

Once a medicine has obtained a marketing authorization, it can in principle be marketed in the countries for which the authorization is valid. However, access to prescription medicines will be limited if they are not at least partially compensated by the national health system through mandatory health insurance. In contrast to marketing authorization, pricing and reimbursement are strictly national competences, although the EU does set an overall regulatory framework, particularly relating to the time it should take to complete pricing and reimbursement procedures (180 days for new medicines and 90 days for generic medicines) (29).

Research has shown that the pricing and reimbursement policies of a country can affect the likelihood of a medicine being launched and the timing of the launch (30-35). These policies can also affect generic competition. In the following sections, we analyse these aspects and their impact on access to medicines in Estonia.

AVAILABILITY OF MEDICINES IN THE ESTONIAN MARKET

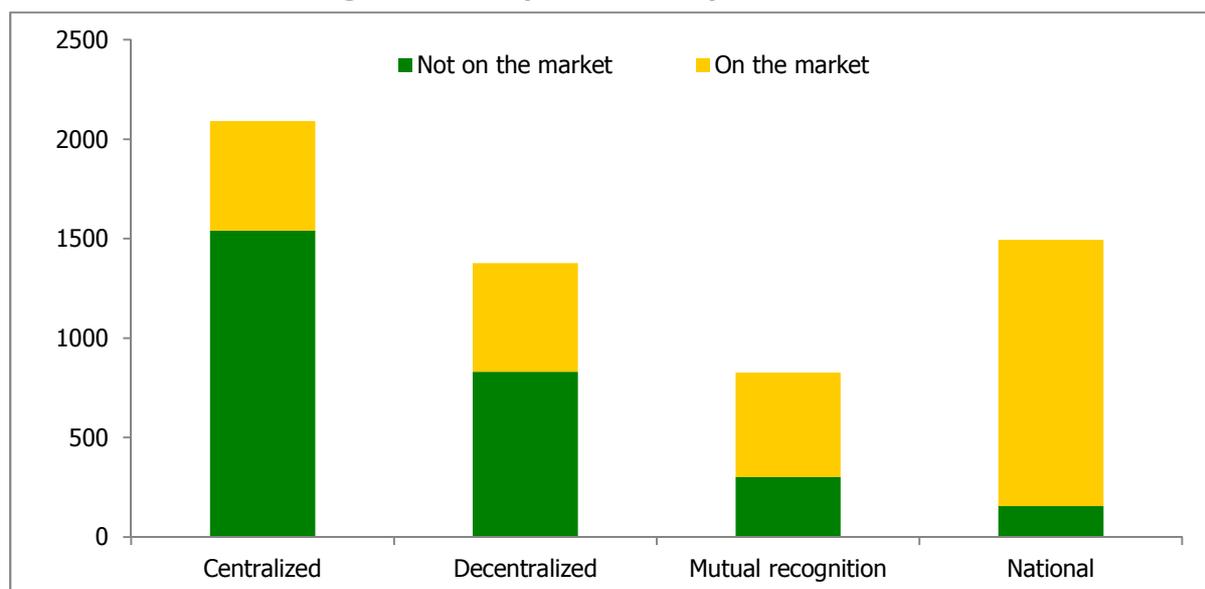
Marketing authorization

Which medicines could potentially be on the market?

Most medicines licensed in Estonia as of March 2015 were authorized through the central EU marketing authorization procedure (total number 2092, with different strengths and formulations counting as different marketing authorizations). A further 1494 were authorized through the national procedure, 1377 through the decentralized procedure and 826 through mutual recognition (Figure

11). However, the fact that a medicine is licensed does not mean it is available on the market. For instance, 74% of centrally authorized products (1540) were not sold on the Estonian market in the past three years. This percentage was lower for those authorized through the decentralized procedure (60%, 831) or mutual recognition (37%, 302), and lowest for nationally authorized medicines (10%, 155). It is not uncommon for companies to register medicines in countries where they do not necessarily intend to market the product. Often the size of the market influences the final decision, but other factors – such as the national administrative procedure for marketing, pricing, taxes, tariffs, distribution mark-ups and lack of an efficient procurement system – also influence the decision (36).

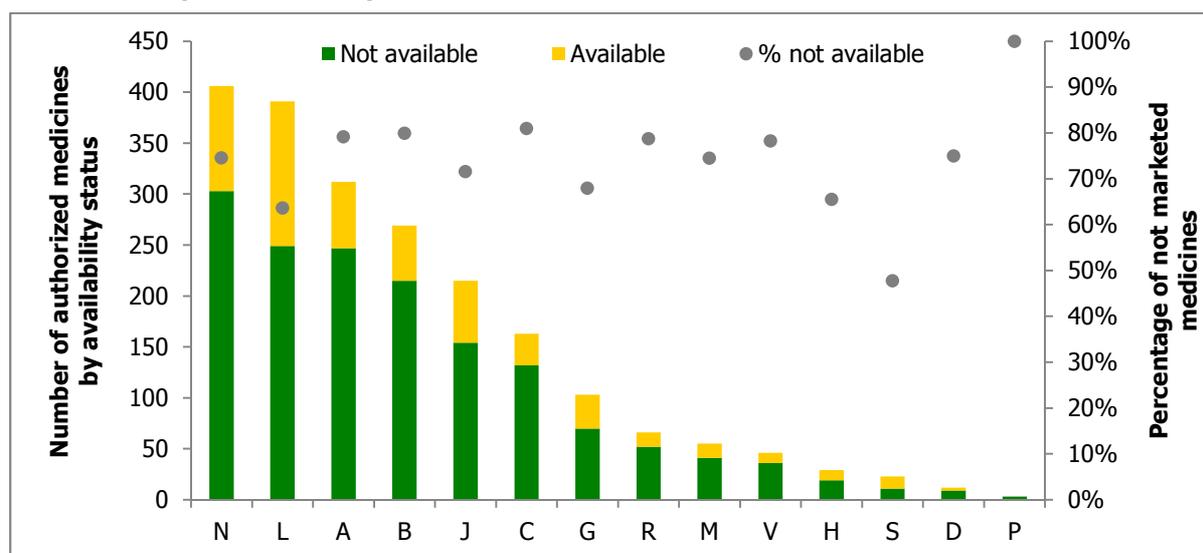
Figure 11. Number of licensed medicines in Estonia in March 2015, by authorization procedure and marketing status in the previous three years^a



^a Different strengths and formulations of the same active ingredient are counted separately, as are different brands.
 Source of data: State Agency of Medicines.

Centrally authorized medicines are interesting, because they allow an assessment of the totality of available medicines and identification of those that are not marketed in Estonia. When marketing authorization was obtained via the decentralized, mutual recognition or national procedure, it is only possible to assess which of the registered medicines are not available, i.e. it is not possible to analyse medicines that are not registered in the country; this may produce a bias towards certain therapeutic groups. Overall, 74% of centrally authorized formulations were not marketed and available in Estonia in the past three years. Most centrally authorized medicines are in the following therapeutic areas: neurological system (anatomical therapeutic chemical (ATC)-N: 406 formulations), antineoplastic and immunomodulating therapies (ATC-L: 391 formulations), alimentary tract and metabolism (ATC-A: 312 formulations), and blood and blood-forming products (ATC-B: 269 formulations) (Figure 12). In absolute terms, the highest number of unavailable products was for ATC-N (303 formulations, 75% of the total in the area), followed by ATC-L (249 formulations, 64% of total), ATC-A (247 formulations, 79% of total) and ATC-B (215 formulations, 80% of total).

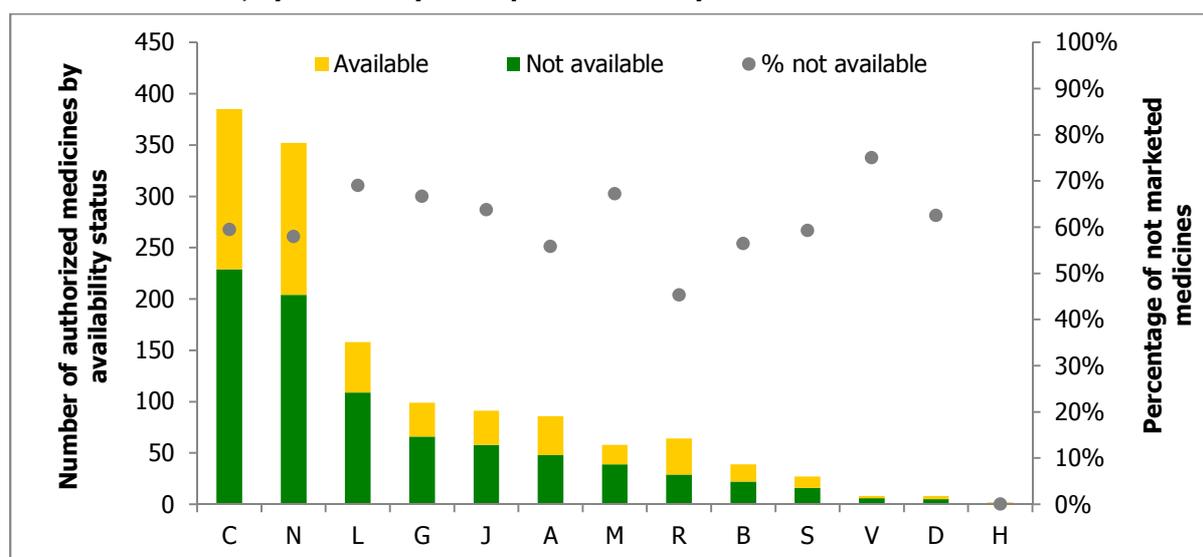
Figure 12. Number of centrally authorized medicines in March 2015, by availability in the previous three years^a



^a The x-axis shows the therapeutic class, according to the WHO ATC classification. Different strengths and formulations of the same active ingredient are counted separately, as are different brands.
 Source of data: State Agency of Medicines.

Overall, 60% of medicines authorized in Estonia through the decentralized procedure were not marketed in the country in the past three years. Most medicines authorized in Estonia through the decentralized procedure targeted the cardiovascular system (ATC-C: 385 formulations) or neurological system (ATC-N: 352 formulations) (Figure 13). These were also the groups with the highest number of unavailable medicines (229 formulations for ATC-C, 59% of total in the area and 204 formulations for ATC-N, 58% of total). As for centrally authorized medicines, ATC-N is among the therapeutic classes with the highest number of registered but also unavailable medicines. A smaller number of ATC-L medicines were authorized through the decentralized procedure and nearly 70% of them were not available.

Figure 13. Number of medicines authorized through the decentralized procedure as of March 2015, by availability in the previous three years^a



^a The x-axis shows the therapeutic class, according to the WHO ATC classification. Different strengths and formulations of the same active ingredient are counted separately, as are different brands.
 Source of data: State Agency of Medicines.

Overall, 37% of medicines authorized in Estonia through the mutual recognition procedure were not marketed in the country in the past three years. The therapeutic classes with most medicines authorized through mutual recognition were, once again, ATC-N (182 formulations) and ATC-C (195 formulations) (Figure 14). In this case, however, fewer than 50% were unavailable (ATC-N: 72 formulations, 40% of total in the class; ATC-C: 62 formulations, 32% of total). In percentage terms, unavailability was highest for ATC-L (17 formulations, 59% of total).

Figure 14. Number of medicines authorized through the mutual recognition procedure as of March 2015, by availability in the previous three years^a



^a The x-axis shows the therapeutic class, according to the WHO ATC classification. Different strengths and formulations of the same active ingredient are counted separately, as are different brands.

Source of data: State Agency of Medicines.

As expected, most medicines authorized through the national procedure were available on the Estonian market in the past three years. Overall, only 10% of registered medicines were not available. In absolute terms, unavailability was highest for ATC-N (36 formulations, 12% of total in the class), ATC-C (31 formulations, 13% of total) and ATC-A (20 formulations, 15% of total) (Figure 15). In percentage terms, unavailability was highest for ATC-L (11 formulations, 18% of total).

Figure 15. Number of medicines authorized through the national procedure as of March 2015, by availability in the previous three years^a



^a The x-axis shows the therapeutic class, according to the WHO ATC classification. Different strengths and formulations of the same active ingredient are counted separately, as are different brands.

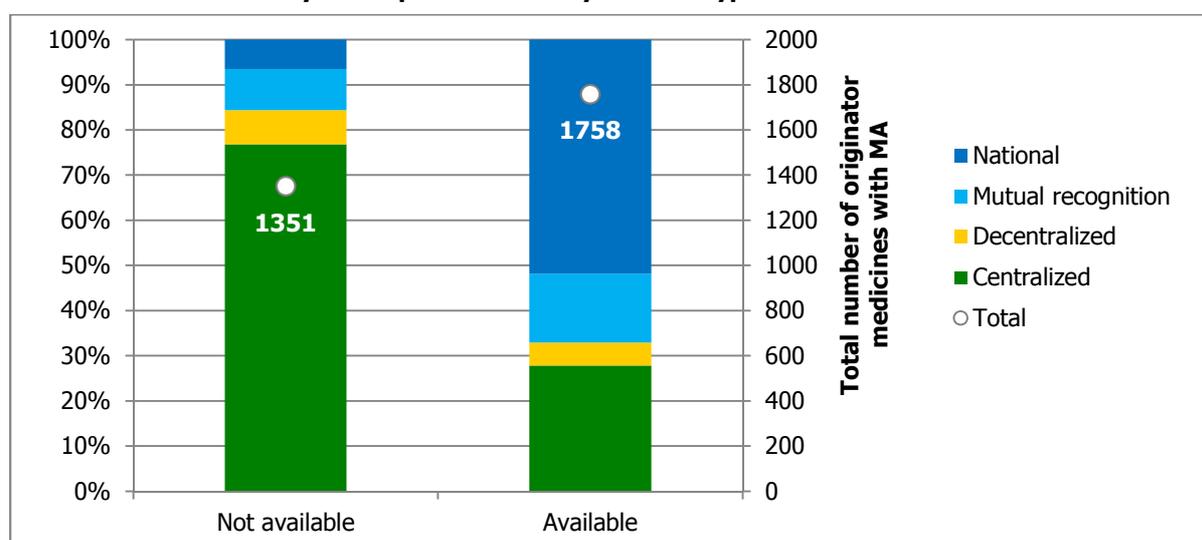
Source of data: State Agency of Medicines.

The figures in this section are for patented and generic medicines combined. The following sections present data for these two groups separately.

On-patent products

As of March 2015, 1351 registered branded medicines had not been available on the market in the previous three years. The majority of non-marketed medicines (77%) had been approved through the centralized procedure, while the majority of marketed medicines (52%) had been approved nationally (Figure 16). This is not surprising given that most new medicines tend to be approved through the centralized procedure.

Figure 16. Number of branded medicines with marketing authorization as of March 2015, by availability in the previous three years and type of authorization^a



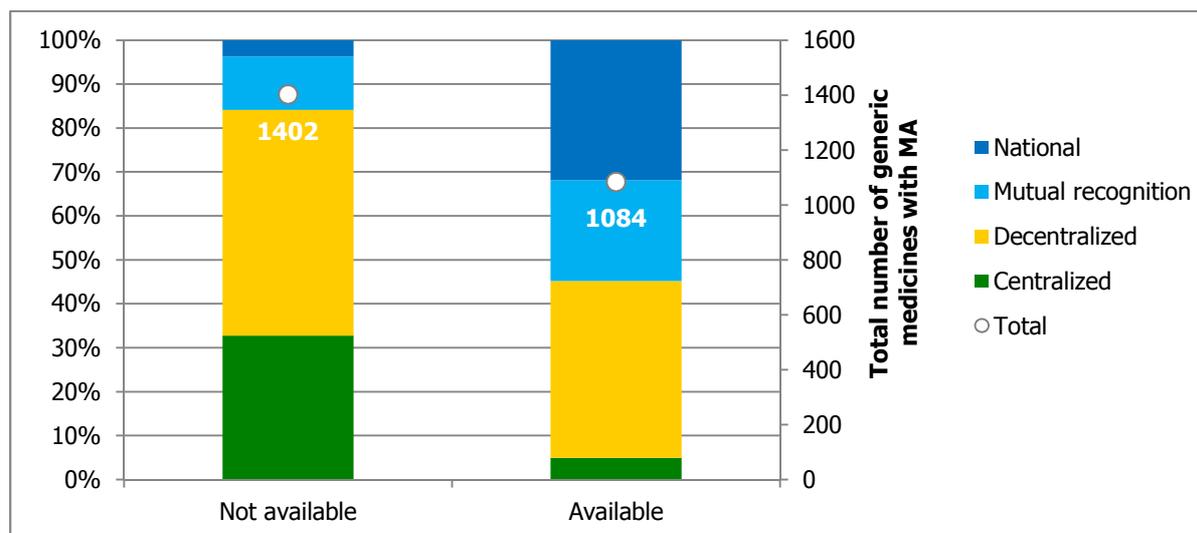
^a Different strengths and formulations of the same active ingredient are counted separately, as are different brands; 194 registered medicines were not included because of lack of information on status (on-patent or generic).

Source of data: State Medicines Agency.

Off-patent medicines

As of March 2015, 1402 registered generic medicines had not been available on the market in the previous three years. The majority of non-marketed medicines (51%) had been approved through the decentralized procedure, with 33% approved through the centralized procedure, while 40% of marketed medicines had been approved through the decentralized procedure, and 32% through the national procedure (Figure 17). Overall, branded medicines were more available than generics (57% vs 44% out of a total of 5595 registered formulations).

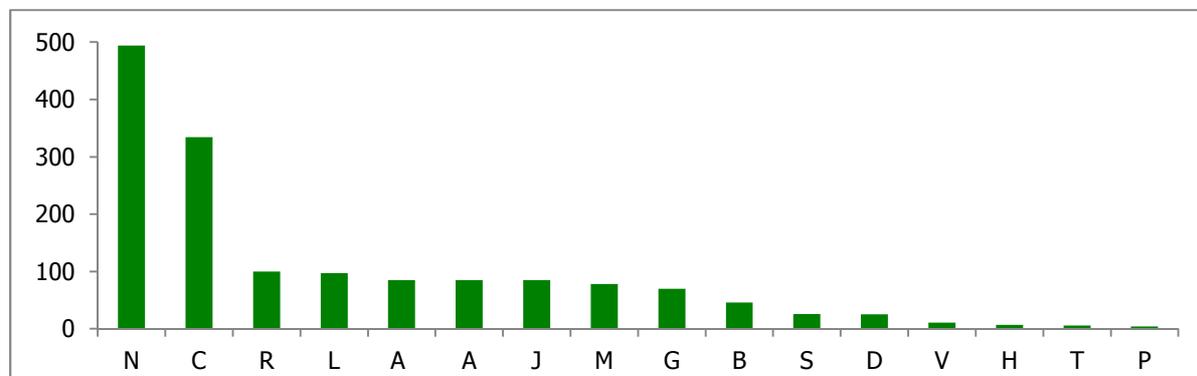
Figure 17. Number of generic medicines with marketing authorization as of March 2015, by availability in the previous three years and type of authorization^a



^a Different strengths and formulations of the same active ingredient are counted separately, as are different brands; 194 registered medicines were not included because of lack of information on status (on-patent or generic).
 Source of data: State Agency of Medicines.

Between 2012 and 2014, the licence for 1553 medicines was not renewed, and they therefore lost their marketing authorization (Figure 18). The largest group of these medicines were those targeting the nervous system (494 formulations), followed by the cardiovascular system (334 formulations), respiratory system (100 formulations), and antineoplastic and immunomodulating products (97 formulations).

Figure 18. Number of medicines for which the licence was not renewed, 2012–14^a



^a Different strengths and formulations of the same active ingredient are counted separately, as are different brands.
 Source of data: State Agency of Medicines.

Individual applications for medicines without marketing authorization

Doctors and professional organizations can make an application to SAM for the use of non-authorized medicines for specific cases or situations.⁵ SAM may grant permission if the case is clinically justified (37). In 2011, there were almost 8000 such applications, covering 110 different active substances, either for the treatment of specific patients or for use within the framework of national programmes

⁵ Doctors may apply for authorization for outpatient use for individual patients or for in-hospital use for the medical institution as a whole, for a maximum of 1 year; professional organizations may apply for use in a cohort of patients.

against tuberculosis and HIV (6). In 2014 there were about 5000 such applications⁶. Non-registered medicinal products account for 2% of the total market for pharmaceuticals in Estonia (6).

According to the Association of Pharmaceutical Manufacturers in Estonia (APME), the market has become so competitive that companies often withdraw their products because they cannot afford to continue paying the annual fee for the licence. However, the annual fee is only €160, which seems rather modest to cause the withdrawal of a product on affordability grounds. While it is not difficult to obtain permission to use a non-authorized product, the challenge is often finding a wholesaler willing to import the medicine.

The marketing authorization process

Assessment times for non-centralized marketing authorization procedures

Table 2 compares the length of time taken to issue marketing authorizations in 2011 and 2014 using the decentralized, mutual recognition and national procedures in Estonia in comparison to prescribed times by EU. While the first two of these procedures remained broadly within the prescribed timeframes (apart from the translation of product information), the national procedure took on average 160 days longer than prescribed in 2014. Nevertheless, it is important to notice that this represents an important improvement in comparison to 2011.

Table 2. Prescribed time for non-centralized marketing authorization procedures in the EU and actual time taken in Estonia in 2011 and 2014

	Prescribed time for assessment + preparation of summary product characteristics (SPC) (days)	Average time for assessment + preparation of SPC (days)	Number of marketing authorizations issued
Decentralized procedure	210 + 30	210 + 46 (2014) 206.9 + 55 (2011)	313 274
Mutual recognition	90 + 30	90 + 46 (2014) 94 + 66 (2011)	46 75
National procedure	210 + 30	370 (2014) 622 (2011)	22 11

Sources of data: prescribed times (European Parliament & The Council, 2012); Estonian data are from the State Agency of Medicines.

Fees

Two types of fee are applicable to non-centralized marketing authorization applications in Estonia: the state fee (paid before the application is submitted) and the assessment fee (paid on submission of a valid application). Although companies complain about these costs, they have never done so in writing; marketing authorization fees in Estonia seem generally to be lower than applicable fees in Latvia and Sweden (Annex 2).

There is also an annual fee for safety and quality monitoring. A marketing authorization holder must pay the State Agency of Medicines a fee of €160 for each marketing authorization valid in the previous calendar year. If Estonia participates in the decentralized or mutual recognition marketing authorization procedure as a reference country, or if the State Agency of Medicines regularly participates as representative of a reference country in the work-sharing procedure of the periodic safety update report of the Coordination Group and Pharmacovigilance Risk Assessment Committee of the European Medicines Agency, the safety and quality monitoring fee for a medicinal product will be €320 for each marketing authorization that was valid for over six months in the previous calendar

⁶ data provided by SAM

year. The State Agency of Medicines may waive the safety and quality monitoring fee if the wholesale figures for the medicinal product during the year are less than €4800 euros and 2000 packages.

Other procedural and regulatory aspects

All relevant information is available in English on SAM's website together with electronic application procedures. In an attempt to promote the Estonian pharmaceutical market, the SAM has a booth at relevant conferences to explain to pharmaceutical companies the procedures for marketing medicinal products in Estonia.

Market entry

Between January 2013 and May 2015, out of 140 medicines that obtained EU marketing authorization, 40 were the subject of applications for reimbursement in Estonia (MoSA, unpublished observations). For 34 medicines, a reimbursement application was not needed: 19 of these were already on the inpatient service list, 13 were used in national programmes and two were lifestyle medicines and thus not eligible for reimbursement. There were, however, 66 medicines for which no application was made – 41 on-patent medicines (including nine for oncology, seven for diabetes and five for the endocrine system) and 25 generic drugs. Of the 40 applications for reimbursement, 21 have been decided; the remaining are still pending. Four applications have passed the deadline for assessment.

Generic competition

Discussions with the MoSA highlighted the issue of limited entry and subsequent exit of generic drugs a few years after marketing authorization is obtained. This often leads to the re-establishment of the monopoly that existed before the patent expired. The MoSA cited the example of tamoxifen, and further analysis was conducted to obtain empirical evidence (see Annex 3). The original medicine, Nolvadex, sells better than the only generic version still on the market, because it has a lower price. However, the manufacturer of generic tamoxifen wants to withdraw the medicine from the market, and the manufacturer of Nolvadex is now asking for a higher price. Suppliers of generic anti-glaucoma medicines have complained that their products do not sell and said that they will need to withdraw them from the market. The MoSA stressed that these issues are dynamic and that the therapeutic classes affected change over time.

Another issue mentioned was the high price of a number of generic medicines in comparison with neighbouring countries. The price of tamoxifen, for example, is lower in Latvia and Lithuania than in Estonia, where patients have a preference for brand-name drugs. The time of entry in the market is also an important factor: if several generic versions of a medicine enter the market at about the same time (e.g. the same quarter when the reference prices are updated), they will each have a very small market share, and may subsequently be withdrawn because of low sales volume. However, if generics are introduced gradually over a longer time period, the process can be better managed and they are more likely to stay on the market. Finally, the inability to supply the entire market may prevent some generics gaining significant market shares. This is likely to have been the case with one of the versions of generic tamoxifen, which was removed from the market.

These issues are compounded by the fact that generic prescribing is not universal: 86% of prescriptions issued by doctors in 2014 were based on the active ingredient (11). Patients' mistrust of generics is still a concern, although the situation is improving thanks to the annual mass information campaigns conducted by EHIF. In addition, patients are often willing to pay out-of-pocket for brand-name medicines.

According to the MoSA, manufacturers are more interested in marketing their medicines and engaging in discussions around the most suitable pack-size and prices if they have a local representative in Estonia, or at least another Baltic country.

Unsustainable pressure on prices through internal reference pricing is causing generic manufacturers to leave the Estonian market, according to the APME. When challenged that a 50% price reduction on the fifth generic is not excessive, the APME said that prices can be up to 70% lower than the on-patent price. Further, if a number of companies are willing to enter the market, the price can be as low as 10% of the on-patent price as a result of IRP. This happened in the case of candesartan and, according to the APME, it is not an exception.

In an attempt to shed some light on complaints of limited availability of generic medicines following patent expiry, we conducted a series of case studies to analyse competition patterns following patent expiry, using the examples of selected cancer medicines (endocrine therapies and imatinib) and glaucoma treatments (see Annex 3 for the results of the analysis). These were chosen on the advice of the MoSA, because of the limited availability of generic alternatives (or – in the case of imatinib – very high availability) and the results may therefore not be readily generalizable. However, the study offers a good snapshot of existing issues in therapeutic groups where there is little competition or a rapid switch to generics after expiry of the patent (imatinib).

For most of the medicines included in our case studies, there is limited generic penetration in the market, which is still dominated by the original drug years after the patent expired. Exemestane, imatinib and timolol are notable exceptions. The facts that generic prescribing is not universal and that generic substitution by pharmacists is not mandatory, together with patient preference and readiness to pay for original drugs, are likely to contribute to this outcome.

A study on determinants of entry of generics in prescription markets in the EU found that price capping policies seemed to have a negative effect on both the extent of price competition and the penetration of generic drugs (38). The frequent adjustment (e.g. every 6 months) of maximum reimbursement prices, initiatives to encourage physicians to prescribe using the international non-proprietary name (INN) (through either regulations, budget restrictions or budget incentives), compulsory generic substitution by pharmacists, reimbursement based on the lowest-priced generic and, to a lesser extent, patient co-payment if the price exceeds the reference price tend to have a positive effect on price competition (38). Penetration of generic medicines is positively influenced by compulsory generic substitution by pharmacists and, to a smaller extent, by the frequent adjustment of maximum reimbursement prices, initiatives to encourage physicians to prescribe using the INN and reimbursement based on the lowest-priced generic (38). The number of producers of the same generic medicine was found to positively affect price competition (38).

As mentioned, the medicines in our case studies (apart from exemestane, imatinib and timolol) were deliberately chosen to represent therapeutic areas with low generic penetration. A study on use of antidepressants in Estonia found that generic penetration for this therapeutic group is on average 60%, and up to 80% for medicines with a large price difference between generic and branded drugs (39). The average price per defined daily dose (DDD) of escitalopram was €1.01 for the branded version and €0.30 for the generic. The branded version accounted for 20% of the total market share (by value) (39). The situation was similar for other selective serotonin reuptake inhibitors (SSRIs). The cheapest generic required a 75% lower patient co-payment than the branded medicine (39). In 2011, half of the new users filled only one prescription (39); 27% of new users who filled two or more prescriptions started treatment with the brand-name product, with half of them later switching to a generic (39).

It seems, therefore, that there are lessons to be learned from positive experiences in therapeutic areas with higher generic penetration.

Potential barriers to launching products in Estonia

Previous studies on branded and generic medicines in a number of countries have found that the following factors affect probability of launch and time to launch: expected price and volume, use of

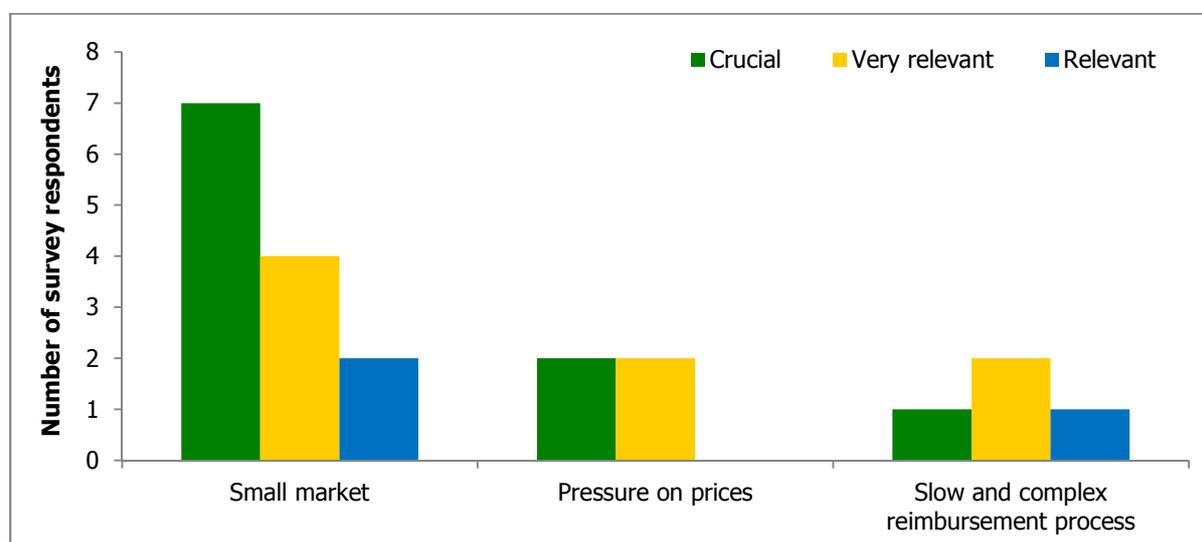
price regulation mechanisms, strength of intellectual property regulation, parallel imports, companies' economies of scale, therapeutic importance of specific product innovations, health expenditure per capita, and measures to promote availability and distribution of medicines, such as having a list of essential medicines and a national formulary (30-35, 40). However, these studies did not distinguish between barriers to applying for a marketing authorization and barriers to marketing of authorized products.

The following paragraphs review the potential barriers that are most relevant in Estonia.

Applying for marketing authorization

In May 2014, SAM conducted a survey of 45 marketing authorization holders and their representatives; 14 of those contacted responded (31%) (41). The survey respondents were asked to suggest reasons why the producer they represented might not apply for a particular marketing authorization in Estonia (Figure 19).

Figure 19. Reasons why manufacturers would not apply for a marketing authorization in Estonia^a



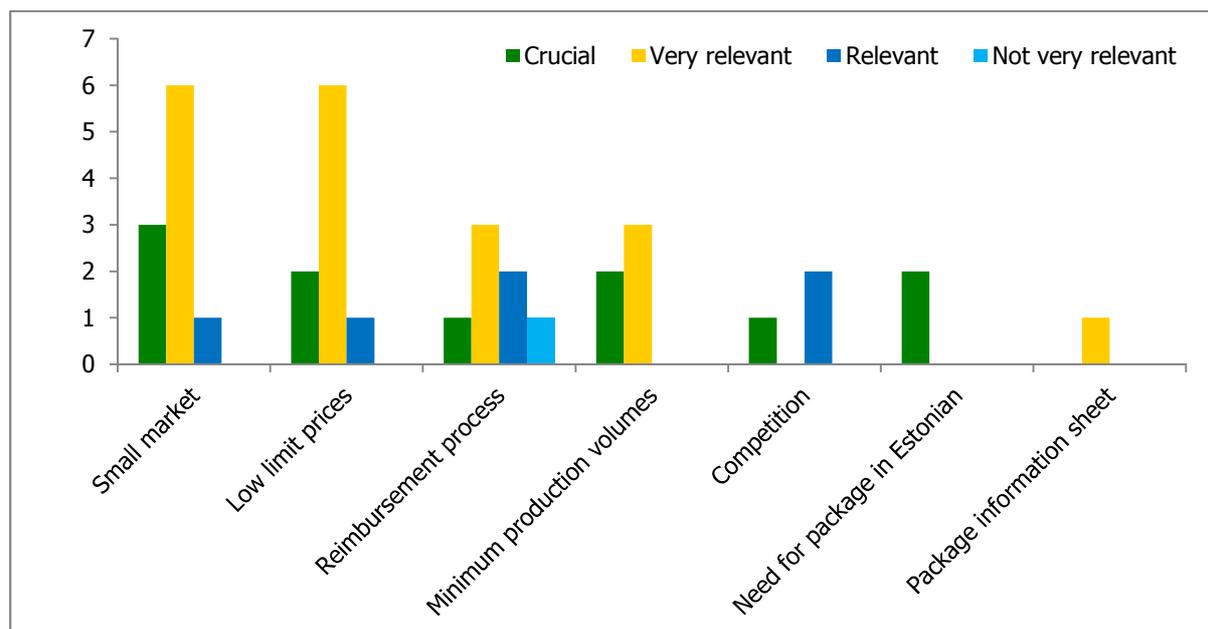
^a Responses from manufacturer representatives in Estonia; one representative may represent more than one manufacturer. Source: SAM survey.

Marketing an authorized medicine in Estonia

When medicines have been authorized via the centralized, mutual recognition (if initiated by the country) or decentralized procedure (if initiated by the country), the manufacturer may never have intended to market the products in Estonia, because of market size and other aspects of the market. As shown previously (Figure 15), most medicines approved through the national procedure are on the market, and any lack of availability is not likely to be related to market size or GDP, since these factors were known at the time of application.

The survey of marketing authorization holders and their representatives discovered concerns about the following factors affecting the likelihood of medicines with a marketing authorization being launched in Estonia: the small market size; the low limit prices imposed by internal reference pricing; the length and complexity of the reimbursement process (also mentioned by the large wholesaler interviewed and the APME); the fact that the market potential is lower than minimum production volumes; tight competition; the need for packaging in Estonian; and the difficulties in reaching consensus among countries over the content of the package information (presumably this refers to the Baltic package) (Figure 20).

Figure 20. Reasons why manufacturers would not launch a medicine that has marketing authorization in Estonia



Source of data: (41).

The requirement for packaging and leaflets in the Estonian language was mentioned as a barrier, especially in the case of medicines with small volumes or small package size (which prevents labelling in more than one language).

The MoSA thinks that the situation with regard to availability of on-patent medicines is clear: if the medicine is reimbursed it is marketed; if it is not reimbursed, it is not marketed. The EHIF and the MoSA have received feedback from manufacturers that they often do not apply for reimbursement because of the likelihood of a negative decision. The EHIF and the MoSA have tried to streamline the process, by allowing manufacturers to submit background information in English, using information from submissions in other countries. Since 2014, they also allow manufacturers of orphan medicines to use cost-effectiveness information from other countries, leaving it to the EHIF to consider local cost and epidemiological data and to adapt the model to Estonian clinical practice. While not specific to on- or off-patent medicines, the large wholesaler thinks that availability issues relate mainly to medicines that are generally less easily available in small markets. This includes, for example, medicines that are registered in the EU for which it is difficult to find a supplier. Another issue is that not all medicines are included in the reimbursement list. The APME stressed the importance of having a local representative in the country to increase the likelihood of launching new products and of having a medicine included in the discount list, which, according to the Association, varies across therapeutic areas. The Association also suggested that a lot of registered medicines are not on the market because they are not needed.

Stakeholders' opinions on how to address existing barriers

The APME is of the opinion that the Estonian market has to become more attractive if entry of EU-approved products is to increase. While market size cannot be changed, the reimbursement process needs to become more transparent, in order to increase the predictability of outcomes. There have been instances when a medicine has been accepted with severe restrictions, which manufacturers have not been prepared to accept. The key ingredients are transparency, speed and price. However, the APME is aware that pressure on prices will not cease, and is therefore of the opinion that the focus should be on transparency (predictability) and speed. Finally, a pharmaceutical policy with a long time perspective is needed.

Respondents to the survey of marketing authorization holders and their representatives offered the following recommendations to encourage more manufacturers to apply for licences and to market their products in Estonia (41).

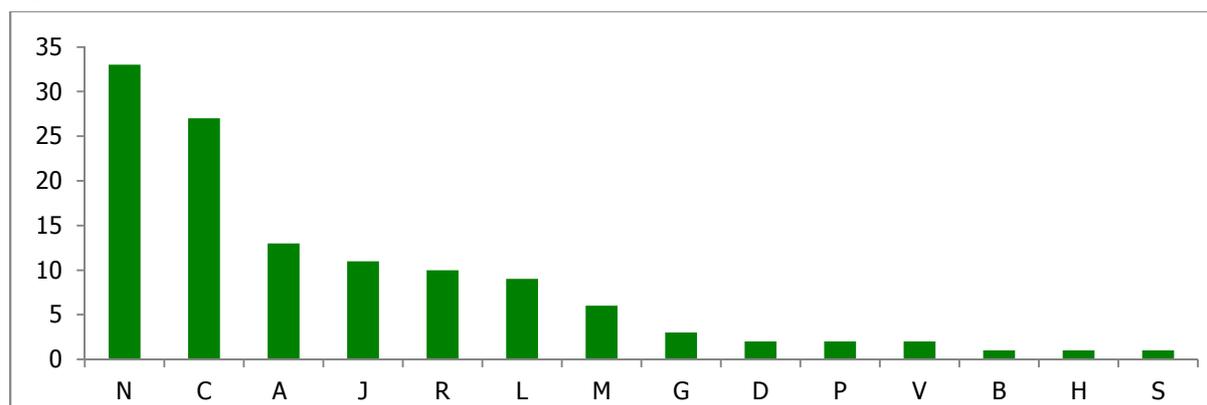
1. Broaden the criteria for including innovative medicines in the reimbursement list. Inclusion should be based not only on budget impact⁷ but also on treatment outcomes. Additional staff are needed to reduce the length of the assessment process.
2. Stop the practice of ERP, because it does not take into account the size and other specific features of the Estonian market. Consider flexible pricing policies, e.g. risk-sharing and clawbacks.
3. Increase the transparency of the reimbursement process.
4. Consider the possibility of re-labelling small-sized medicines in the Estonian language (i.e. translating labels produced in another language according to good manufacturing practices (GMP)), rather than asking for a specific Estonian package. Simplify labelling requirements for small-volume medicines and hospital packages. For orphan medicines, consider using foreign language packages, without the need to register the repackaging.
5. Update clinical guidelines to reflect clinical practice in Estonia.
6. Split the market between the winner of a tender bid (80%) and the second in line (20%).

As noted by SAM, medicines used in hospitals, vaccines and radiopharmaceuticals do not need to have Estonian-language packaging; also, foreign-language packaging is permitted for medicines that are not marketed in Estonia in the particular formulation (41). Orphan medicines do not need to have an Estonian-language package, although in this case exceptions have to be approved by the European Medicines Agency (41).

Shortages

In 2012, the European Medicines Information Network (EMI-net) working group on shortages of medicines in small markets conducted a survey among selected small EU markets⁸ to assess the extent of the problem and formulate policy recommendations (42). Data on medicine shortages collected by SAM showed that the most affected therapeutic areas in Estonia were neurological and cardiovascular treatments (together accounting for about 50% of all notified shortages) (Figure 21).

Figure 21. Number of medicines in shortage in Estonia in 2009–2012^a



^a ATC classification: A: alimentary tract and metabolism; B: blood and blood-forming organs; C: cardiovascular system; D: dermatologicals; G: genitourinary system and sex hormones; H: systemic hormonal preparations, excluding sex hormones and insulins; J: anti-infectives for systemic use; L: antineoplastic and immunomodulating agents; M: musculoskeletal system; N: nervous system; R: respiratory system; S: sensory organs; V: various.

⁷ The EHIF and the MoSA maintain that cost-effectiveness, rather than budget impact, is the key decision criterion. However, it seems that industry representatives perceive budget impact as the main criterion.

⁸ Cyprus, Estonia, Iceland, Latvia, Lithuania, Malta and Slovenia.

Source: data on medicine shortages collected by SAM.

The European Association of Hospital Pharmacists conducted a pan-European survey of shortage of medicines in hospitals between March and May 2014. A total of 15 responses were received from Estonia. According to the survey respondents, the medicines most commonly in short supply in Estonia were unlicensed medicines (63.6%, n=11), followed by brand-name medicines and generics. The area of medicine in which the respondent hospitals most commonly experienced shortages was emergency medicine (63.6%, n=7 in Estonia, survey average 30.4%). The greatest number of responses and highest prevalence of supply difficulties from wholesalers were seen in Ireland (88.2%, n=30), Serbia (78.7%, n=14), Estonia (100%, n=10), Poland (77.8%, n=9), and Norway (100%, n=9) (43).

According to SAM, there are about 100 notifications of shortages per year, relating to both generic and branded medicines. SAM hosts an early warning database so that manufacturers can arrange timely import of needed medicines. However, shortages do not seem to be the main issue when it comes to availability. Further, legislation allows a temporary export ban to be imposed on public health grounds, which is a safety measure not all European countries have.

Potential barriers to keeping products on the market

Our meetings with local stakeholders suggested that shortages are not a major issue. If shortages happen, they are temporary and are due to demand and supply issues linked to changes in reference pricing. Frequent updates in reference pricing may lead to problems with availability of generics. However, discussions with stakeholders did not reveal any instances when a therapeutic need was not met. An appropriate substitute can usually be found.

The survey of manufacturers' representatives highlighted that shortages could occur as a result of the need to supply larger markets first, specifically in the case of an international shortage due to higher than forecasted demand, small production volumes of older medicines, and quality and production issues resulting from complex manufacturing processes (e.g. for vaccines) (41). Issues specific to Estonia include the short time between tender award and inventory planning, difficulty of reaching consensus on multi-language packages, need for new medicines to have a package in Estonian only, small volumes, parallel export and manufacturers' supply policies (41).

Currently, wholesalers and pharmacies are required to have products within the IRP in stock; however, they cannot accumulate stock because the reference price changes every few months. If demand suddenly rises, there could be potential supply problems, as confirmed by the APME.

Making longer-term agreements for outpatient tendering, as in Denmark, was a priority for the large wholesaler interviewed, who also thought that state authorities need to be more proactive in establishing contacts regarding products that are not on the market (an activity already conducted on a daily basis by SAM). Another issue, which can occur but seems to be infrequent, is that some small generic companies may enter the market with very low prices, which can lead to shortages if they do not have the capacity to deliver sufficient volume.

According to the APME, the occasional occurrence of shortages is difficult to solve because Estonia is a small country where there is volatility in terms of quantities needed and a lack of parallel traders.

BIOSIMILAR AND ORPHAN MEDICINES

Regarding orphan medicines, the EHIF recognized that they can accept a cost of more than 3 times GDP per QALY, but expressed concern about the need for a full application in such cases. Estonia is such a small country and there may be only one patient with a particular rare disease. For orphan medicines with only one or two patients, it is just not worth applying for a general authorization. Although managing individual applications is not ideal, this is probably the way forward for most orphan medicines. This view was shared by the APME who, in contrast to EHIF, also supports the idea of an earmarked fund for orphan medicines.

As access to biological products will be of increasing importance in the future and as biosimilars⁹ increasingly become available, it will be important to ensure penetration and uptake of biosimilars. While the Estonian authorities have so far not released an official position paper or policy document on biosimilars, as some other countries have done (44-46), there is a clear provision in the health care services list that every new patient starting a biological treatment for ulcerative colitis, Crohn disease, rheumatoid disease or psoriasis has to be given a biosimilar, unless this is contraindicated on medical grounds. Substitution is not prohibited if done by the physician. From the perspective of avoiding co-payments for patients, prescribing of biosimilars is incentivized by internal reference pricing whereby only the two least expensive medicines in any given ATC-5 class are fully reimbursed.

DISCUSSION

While the authorities have made efforts to simplify some processes, many hurdles remain, particularly in the pricing and reimbursement process. We were not provided concrete evidence that anything is being done to address these problems, other than a commitment to train more staff. However, assessment times were shortened between 2011 and 2014, mainly as a result of shorter discussion times in the Committee for Medicinal Products and a shorter time needed to finalize the new directive. The key bottleneck is the assessment by SAM of medical need, availability of alternative treatments, efficacy, safety, utilization of the current product and alternatives in Estonia and other countries, potential for use and misuse, and rational use. The underlying issue appears to be insufficient funding to hire additional staff.

There seems to be a belief that there are barriers in Estonia that are not present in other countries, or that other countries may have some unknown approach that enables them to obtain better prices and more medicines on the market. While there are some barriers that can be addressed (e.g. length of the assessment time), the important factor is a more proactive attitude by all parties involved towards existing problems and action-oriented dialogue with all stakeholders. We were informed that the MoSA is doing some horizon scanning.¹⁰ However, it seems that a “pull” effect and proactive planning are missing (e.g. how many generics and which products are needed?). Sometimes the “push” comes from doctors; an example is biological treatment of rheumatoid arthritis.

Various steps in the right direction have already been taken, but need to be strengthened. The survey of manufacturers conducted by SAM, for example, showed an interest in listening to other views and

⁹ A similar biological or biosimilar medicine is a biological medicine that is similar to another biological medicine that has already been authorized for use. Biological medicines are medicines that are made by, or derived from, a biological source, such as a bacterium or yeast (33).

¹⁰ Horizon scanning is the process of collecting information on innovative technologies in health care in order to support decision-making and the adoption and use of effective, useful and safe health-related technologies (<http://www.euroscan.org/>).

in a proactive approach. Authorities also meet with industry; for example, SAM meets with the APME at least once a year to discuss regulatory issues around marketing authorizations, while the EHIF has 10–20 pre-submission meetings with marketing authorization holders each year. These meetings tend to involve only one public authority and the APME or individual manufacturers, to discuss often very specific issues (e.g. a submission). A multistakeholder dialogue to develop a comprehensive medicine policy took place in 2012–13, and a policy document was drafted and discussed. Despite the promising start, the meetings were discontinued. Such a dialogue should be resumed to identify issues and possible solutions but, most importantly, to agree on a common roadmap to address existing issues. More collaboration with other countries through existing networks, such as the Pharmaceutical Pricing and Reimbursement Information (PPRI) initiative and the Piperska group, and an open discussion of existing problems are also needed. At the moment there seems almost to be a fear of letting other countries know that Estonia is facing certain challenges, even though these are likely also to affect other EU countries.

In general, there seems to be little dialogue among the different stakeholders, public and private, with an interest in improving access to medicine. This is not just true between public and private sectors but applies also to a certain extent within the public sector itself and when it comes to sharing experiences with other countries.

The authorities seem to be simply waiting for companies to apply for pricing and reimbursement. In other countries, companies may be invited to apply. The Scottish Medicines Consortium, for example, may proactively invite companies to submit an application even for a product that has not yet obtained a licence (the review process, however, will only start once a valid marketing authorization has been obtained) (47).

The Baltic package, which is in principle a good approach to address the issue of small volumes, has not delivered the expected results. One issue is certainly the need to have the same text written in three different languages, which means that the three Baltic states have to agree on the content. Experience has shown that this can be a lengthy and tedious process. It was suggested that some flexibility should be allowed, for example, if one country wants to add mention of another side-effect. Another issue is that the Baltic package, and multi-language labelling in general, are not possible for some small-package pharmaceuticals. This does not mean that multi-language labelling should not be pursued, but that compromises need to be found to make it work.

Wholesalers only buy medicines after securing a tender order. This could potentially be a barrier to small generic companies entering the Estonian market, as a contact with wholesalers is needed.

Finally, expectations of what can be achieved at current spending levels need to be realistic. Estonia spent only 6.0% of its GDP on health in 2013 (OECD average 8.9%, EU average 9.52%), and although the country's economy has grown rapidly in the past 15 years, the GDP per capita in 2013 was still below the OECD average and EU average (Estonia US\$ 25 823 vs OECD average US\$ 38 123 vs EU average US\$ 35 295 at PPP current), (12, 48)¹¹; this means that Estonia is spending substantially less on health than the OECD and EU average, even when purchasing power parity is taken into account.

Limitations

This assessment was based on a two-day mission in Tallinn, Estonia, with subsequent data analysis and follow-up with competent authorities. A key limitation of the study relates to the analysis of availability of medicines. Ideally, this should have been conducted on the basis of INN, rather than

¹¹ Data for Estonia and OECD average are taken from the OECD database, EU average data from the WHO health for all (HFA) database. There are minor differences between the OECD and WHO estimates for Estonia. For example, in 2013 health spending as a percentage of GDP was 6.0 in the OECD database and 5.72 in the HFA database.

brand–strength–formulation. However, at the time of the analysis, these were the only data available. It was recognized during the interviews that it is not clear whether there is an unmet therapeutic need as a result of non-entry or delayed entry of new medicines. As is currently widely debated in the literature, many new medicines are “me-too” products, with little added therapeutic value. Non-availability of products with little added therapeutic value means more funds available to invest in areas of where greater health gains are possible, not just on the treatment side but also prevention and palliation side. It would be important to conduct a study to link availability to indicators of therapeutic added value, to gauge whether an actual medical need gap exists in some therapeutic areas. Another limitation of this study is that we were not able to meet with the association of pharmacists, so could not include their views in our assessment. Further, time constraints meant that we could meet with only one large and one small wholesaler.

RECOMMENDATIONS

A common vision and roadmap

- Resume the national multistakeholder policy dialogue started in 2012–13, which included the MoSA, the EHIF, SAM, the APME, and other relevant stakeholders, to define areas of work to improve access to medicines. Include this in the national medicines policy.
- Within the policy dialogue, set up working groups to take specific issues forward.
- The updating of the national medicines policy offers an ideal opportunity to develop a common vision and a road map linked with specific objectives, concrete actions, targets, and a monitoring plan, with clear lines of accountability.
- Establish a multistakeholder mechanism to oversee the implementation of the medicines policy and provide a platform for regular discussion of issues related to medicines.
- Establish which medicines are needed to address the main public health needs of Estonia, including both on-patent and off-patent medicines, and work with other stakeholders in the multistakeholder dialogue towards increasing their availability
- Evidence is needed to inform decision-making and action, for example, studies on prescribing practices particularly for patients with multiple morbidities moving across different levels of care, determinants of generic penetration across different disease areas and whether non-entry or delayed entry of new medicines is causing an avoidable therapeutic gap should be conducted for selected therapeutic areas.
- Proactively invite manufacturers to make a submission for reimbursement of medicines considered of high public health importance. Take measures (including providing increased funding for staff) to ensure that assessment times are within those prescribed by the EU Transparency Directive.

Sharing experiences

- Enhance experience-sharing and increase collaboration with other Baltic countries in areas relevant to availability of medicines (in particular in the areas of market entry, generic competition and strategic procurement); consider similar collaboration with the Nordic countries.
- Expand collaboration with other countries in the area of health technology assessment (HTA) and use of medicines using existing networks (e.g. EUnetHTA, advance-HTA, Piperska).

Addressing procedural barriers

- Explore options to further reduce the time needed for assessment by SAM, the discussions of the Committee for Medicinal Products and the finalization of the Ministerial directive.
- Consider allowing manufacturers to bid as well as wholesalers
- Conduct regular procurement reviews (e.g. ABC analysis) and use the findings to improve procurement practices and generate efficiencies through improved bidding environment
- Discuss with hospital managers and doctors their concerns relating to implementation of joint calls for tender for medicines. Use evidence from other countries to demonstrate the benefits that are likely to accrue for the patients and the health care system. (The Norwegian hospital procurement system, drug procurement cooperation (LIS), is a good example (1).)
- If a medicine deemed important to address the health needs of a sizeable group Estonian patients does not have an EU-wide marketing authorization, proactively seek approval through the decentralized or mutual recognition procedure, which have been shown to be the fastest channels. For small groups of patients it may be less individual patient request may be a better solution.

Promoting use of generics and biosimilars

- Introduce mandatory generic substitution at pharmacy level.
- Continue the campaigns to raise patients' awareness about generics and INN prescribing. Include also information on biosimilars.

Quality use of medicines¹²

- Identify suitable indicators and conduct prescribing audits using data from the e-prescribing system to incentivise evidence-based prescribing by providing feedback to physicians
- Identify what the role of different actors in health sector should be in coordinating pharmaceutical care of patients with multiple morbidities
- Strengthen collaboration between the doctor and the pharmacist in delivering high quality pharmaceutical care and promoting quality use of medicines

Orphan medicines

Discuss the feasibility of implementing existing proposals to increase availability of orphan medicines, including the increased use of individual patient funding requests, HTA and labelling requirements within the multistakeholder dialogue.

Evidence for decision-making

- Leverage on the wealth of high quality data available – possibly in collaboration with the University of Tartu - on use of medicines to conduct analysis to drive policy action and improve pharmaceutical care.

Long-term vision

- Strengthen the use of horizon scanning and targeted proactive planning of pharmacotherapeutic needs.
- Increase expenditure on health and medicines in order to increase access to new medicines. Avoid jeopardizing adequate salaries for hospital health professionals in favour of procurement of hospital medicines.

¹² The scope of this report was to review availability of medicines and the methodology did not seek to specifically address issues related to quality use of medicines. Nevertheless, making cost-effective medicines available without improving the quality of their use is not going to reach one of the three key goals of a health system- as defined by WHO Health System Performance Framework- which is to improve health outcomes for the population it serves.

ANNEX 1. MISSION AGENDA

Thursday, 19 February 2015

9:00 – 10:00	Meeting, WHO country office: briefing and practicalities	Marge Reinap, Head of the WHO Country Office in Estonia Venue: WHO Country Office
10:00 – 12:00	Meeting, Medicines Department, Ministry of Social Affairs: presenting and discussing the evidence of the problems	Dagmar Rüütel, Head, Medicines Department, MoSA Katrin Pudersell, Chief Specialist, Medicines Department Venue: WHO Country Office
13:00 – 14:30	Meeting, State Agency of Medicines	Kristin Raudsepp, Head, State Agency of Medicines Venue: Skype
15:00 – 16:15	Meeting, Health Insurance Fund	Erki Laidmäe, Head of the Pharmaceutical Department Venue: Lembitu 10, Tallinn
16:30 – 18:00	Meeting, Association of Pharmaceutical Manufacturers in Estonia (APME)	Riho Tapfer Venue: J. Poska 51, Tallinn

Friday, 20 February 2015

9:00 – 10:15	Meeting with small wholesale company	Taavo Kivistik, Oriola Venue: Tammsaare tee 47, 4. Korrus
10:30 – 11:45	Meeting with representative of large wholesale company and pharmacy chain	Tiina Kadak, OÜ Tamro Venue: Pärnu maantee 501, 76401 Harjumaa
14:00 – 16:00	Wrap-up and discussion of terms of reference and next steps with MoSA	Venue: WHO Country Office

Two other meetings were envisaged in the original programme (with a parallel importer and with the Association of Pharmacies), but could not take place because the invitees declined to meet the team.

ANNEX 2. MARKETING AUTHORIZATION FEES^A

Country	Type of application	Fee (€)
National procedure		
Estonia	Complete application, one human medicinal product	1,275
	Abridged application, per product	958
	Subsequent pharmaceutical form or strength containing the same active ingredient of the same future marketing authorization holder	511
Latvia	First submitted pharmaceutical form:	
	• new active substance	5,691
	• known active substance, fixed combination, similar biological medicinal products or medicinal product with well established medicinal use	4,269
	• essentially similar medicinal product - generic medicinal product, hybrid application or other application	4,269
	Each additional:	
	• pharmaceutical form or substitution of active substance with a different salt, ester complex or isomer, if it does not differ significantly in properties with regard to safety and efficacy	2,846
	• strength or packaging of medicinal product, including substitution of active substance with a different salt, ester complex or isomer, if it does not differ significantly in properties with regard to safety and efficacy, as well as each application for medicinal product with identical authorization documentation, but with different invented name and with the same or a different marketing authorization holder	1,423
Sweden	Complete application ^b	42,880
	Application concerning a generic medicinal product where the reference medicinal product is not authorized in Sweden (includes hybrid and biosimilar medicinal products)	42,880
	Abridged application (generic, hybrid or biosimilar medical product) where the reference medicinal product is authorized in Sweden	21,440
	Duplicate application	3,216
Mutual recognition and decentralized procedures		
The country is the reference Member State		
Estonia	Additional fee to cover the participation of the State Agency of Medicines in the mutual recognition procedure or decentralized procedure as reference Member State	14,000
Latvia	Expertise on documentation for marketing authorization of medicinal products in the mutual recognition procedure	
	• first submitted pharmaceutical form	2,846
	• each additional pharmaceutical form application	1,707
	• each additional strength or packaging of medicinal product, as well as each application for a medicinal product with identical authorization documentation, but with different invented name and with the same or a different marketing authorization holder	854

	For procedure	
	• initial mutual recognition procedure	5,674
	• repeat mutual recognition procedure	3,544
	Expertise on application and additional documentation for marketing authorization of medicinal products in the decentralized procedure	
	<i>First submitted pharmaceutical form</i>	
	• new active substance	14,229
	• known active substance, fixed combination, similar biological medicinal product or medicinal product with well established medicinal use	5,691
	• essentially similar medicinal product – generic medicinal product, hybrid application or other application	4,269
	<i>Each additional</i>	
	• pharmaceutical form	2,846
	• strength or packaging of medicinal product, as well as each application for medicinal product with identical authorization documentation, but with different invented name and with the same or a different marketing authorization holder	1,423
	<i>For procedure</i>	9,923
Sweden	Additional fee for approval of marketing authorization for a medicinal product through the mutual recognition procedure or decentralized_procedure: ^b	
	• complete application	21,400
	• abridged application	21,400
	• duplicate application (the application must be a duplicate in both Sweden and the concerned Member States)	3,216
<hr/>		
	The country is the concerned Member State	
Estonia	Complete application, fee per one human medicinal product	1,275
	Abridged application, fee per product	958
	Subsequent pharmaceutical form or strength containing the same active ingredient of the same future marketing authorisation holder	511
Latvia	Expertise on application and additional documentation for marketing authorization of medicinal products in the mutual recognition procedure:	
	• first submitted pharmaceutical form	2,846
	• each additional pharmaceutical form application	1,423
	• each additional strength or packaging of medicinal product, as well as each application for a medicinal product with identical authorization documentation, but with different invented name and with the same or a different marketing authorization holder	711
	Expertise on application and additional documentation for marketing authorization of medicinal products in the decentralized procedure:	
	• first submitted pharmaceutical form	4,269
	• each additional pharmaceutical form application	2,846
	• each additional strength or packaging of medicinal product, as well as each application for a medicinal product with identical authorization documentation, but with different invented name and with the same or a different marketing authorization holder	1,423

Sweden	Approval of marketing authorization for medicinal product ^b	
	Complete application	10,720
	Application concerning a generic medicinal product where the reference medicinal product is not authorized in Sweden (includes hybrid and biosimilar medicinal products)	10,720
	Abridged application (generic, hybrid or biosimilar medical product) where the reference medicinal product is authorized in Sweden	6,968
	Duplicate application	3,216
Renewal fee		
Estonia	For one medicinal product	639
	Subsequent pharmaceutical form or strength containing the same active ingredient of the same future marketing authorization holder	383
	Additional fee to cover the participation of the State Agency of Medicines in the mutual recognition procedure or decentralized procedure as reference Member State	3,000
	Latvia	
Expertise on application and additional documentation for renewal of marketing authorization of medicinal product authorized in the national procedure		
<ul style="list-style-type: none"> • one pharmaceutical form 	2,134	
<ul style="list-style-type: none"> • each additional pharmaceutical form 	1,138	
<ul style="list-style-type: none"> • each additional strength or packaging of medicinal product, as well as each application for a medicinal product with identical authorization documentation, but with different invented name and with the same or a different marketing authorization holder 	711	
Expertise on application and additional documentation for renewal of marketing authorization of medicinal product in the mutual recognition and decentralized procedure:		
<i>Reference Member State</i>		
<ul style="list-style-type: none"> • single pharmaceutical form 	2,846	
<ul style="list-style-type: none"> • each additional pharmaceutical form 	1,423	
<ul style="list-style-type: none"> • each additional strength or packaging of medicinal product, as well as each application for a medicinal product with identical authorization documentation, but with different invented name and with the same or a different marketing authorization holder 	711	
For procedure	4,269	
<i>Concerned Member State</i>		
<ul style="list-style-type: none"> • first submitted pharmaceutical form 	2,846	
<ul style="list-style-type: none"> • each additional pharmaceutical form application 	1,423	
<ul style="list-style-type: none"> • each additional strength or packaging of medicinal product, as well as each application for a medicinal product with identical authorization documentation, but with different invented name and with the same or a different marketing authorization holder 	711	
Sweden	Included in the annual fee	

<i>Annual fee</i>		
Estonia	Annual fee for monitoring of safety and quality	160
Latvia	Post-authorization maintenance fee (annual) for each authorized pharmaceutical form and strength	498
Sweden	Human medicinal product	4,931
	Additional strength or pharmaceutical form	2,412
	Duplicate	2,412

^a Fees rounded to whole digits. Exchange rate for Sweden: 1 Swedish krona = €0.1072 (European Central Bank, 29 May 2015).

^b The fee covers all routes of administration, strengths and pharmaceutical forms of the same medicinal product (trade name) applied for at the same time.

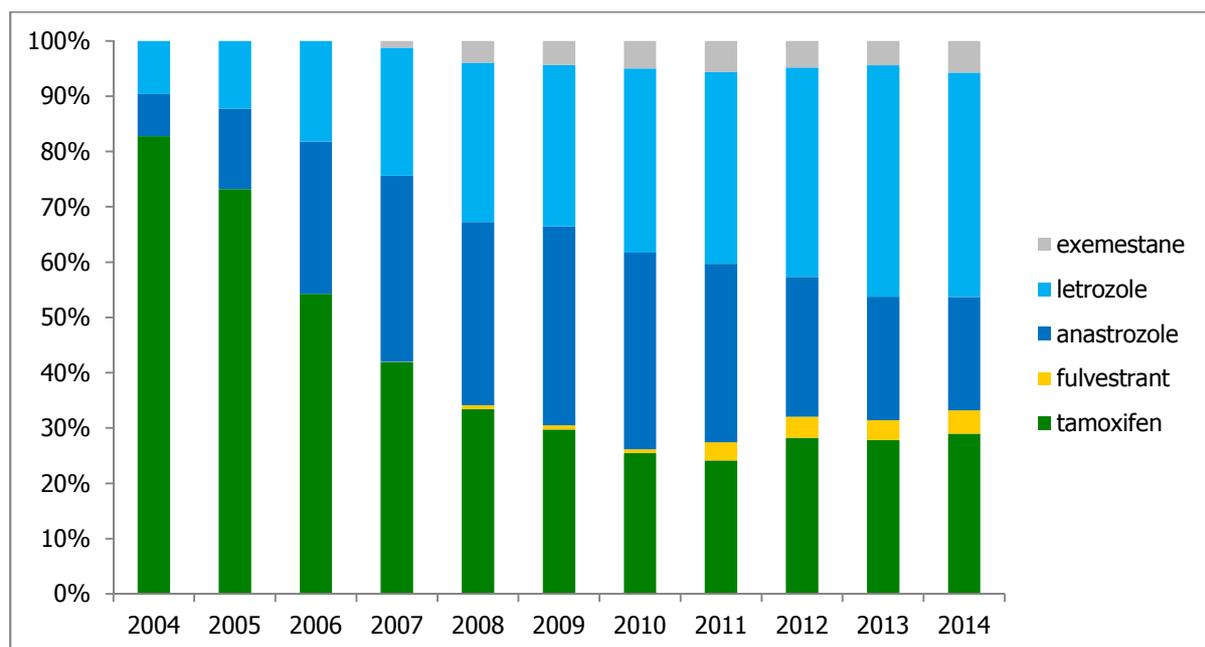
Sources of data: (49-51)

ANNEX 3. CASE STUDY ON GENERIC COMPETITION

Endocrine therapies for breast cancer

There are two main types of endocrine therapy for breast cancer – anti-estrogens and aromatase inhibitors. The former group includes tamoxifen, toremifene and fulvestrant while the latter aminoglutethimide, formestane, anastrozole, letrozole, vorozole and exemestane. Figure A3.1 shows how the use of the different endocrine therapies evolved in Estonia between 2004 and 2014. As in other countries (52), consumption of tamoxifen decreased between 2004 and 2011 in favour of anastrozole and letrozole, with a more recent increase in consumption of tamoxifen because of evidence of side-effects linked with the two aromatase inhibitors.

Figure A3.1. Percentage volume of different endocrine therapies used in Estonia, 2004–2014^a



^a Data for 2004–05 cover only the outpatient sector. In Estonia, most of these medicines are dispensed and consumed in outpatient settings.

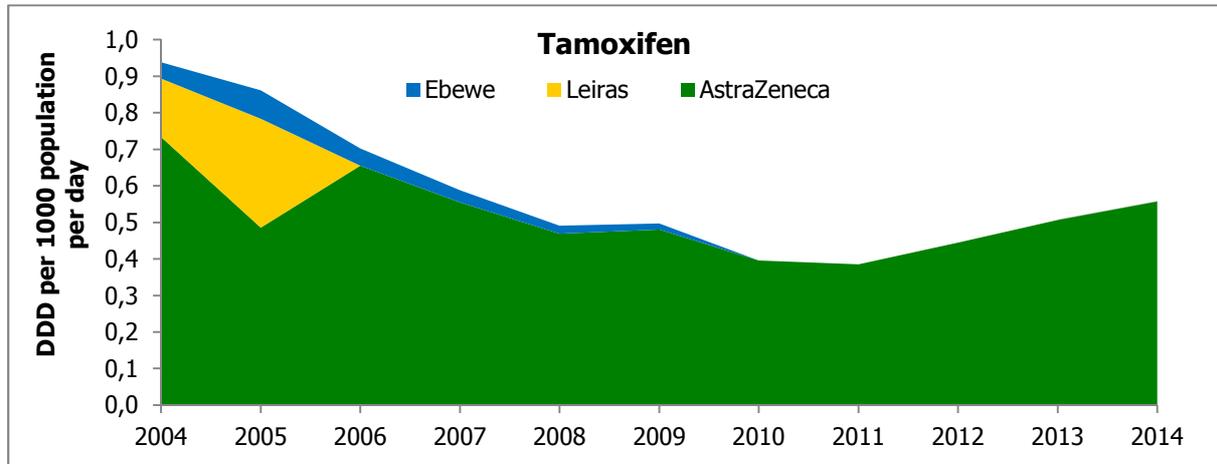
Source: based on data from the EHIF, analysis by the authors.

The following figures show consumption of individual medicines (DDD per 1000 population per day and percentage volume). Apart from the case of exemestane, the branded medicine remained dominant even years after the first generic entered the market.

In 2005, the two generic versions of tamoxifen, produced by Leiras and Ebewe, had together close to 50% market share (Figure A3.2). Another generic version, Zitazonium, was registered and used in reference pricing, but was never marketed. In 2006, Leiras withdrew its product from the market; the market share of Ebewe steadily decreased until 2010, when only the AstraZeneca product was left on the market.

Figure A3.2. Consumption of different trade names of tamoxifen in Estonia, 2004–2014. A: DDDs; B: by percentage volume

A.



B.

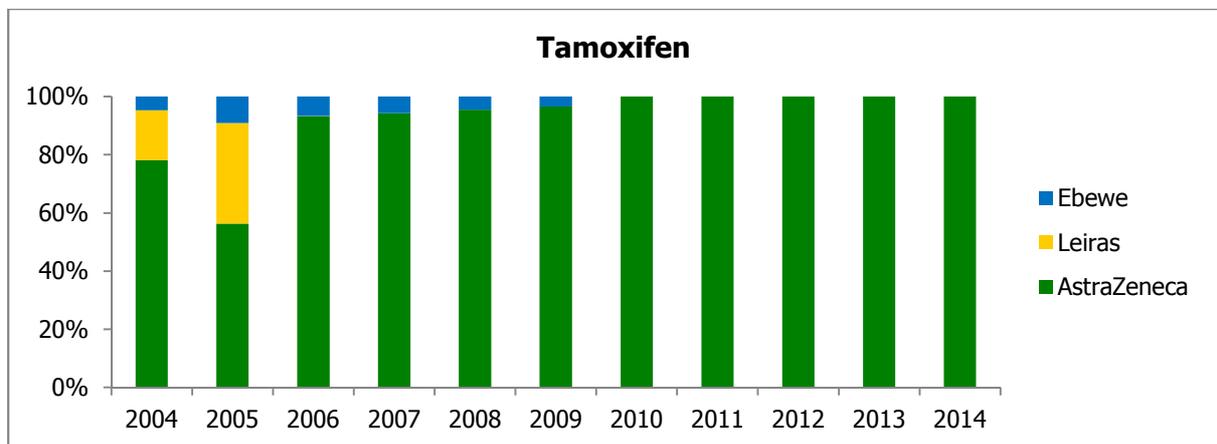
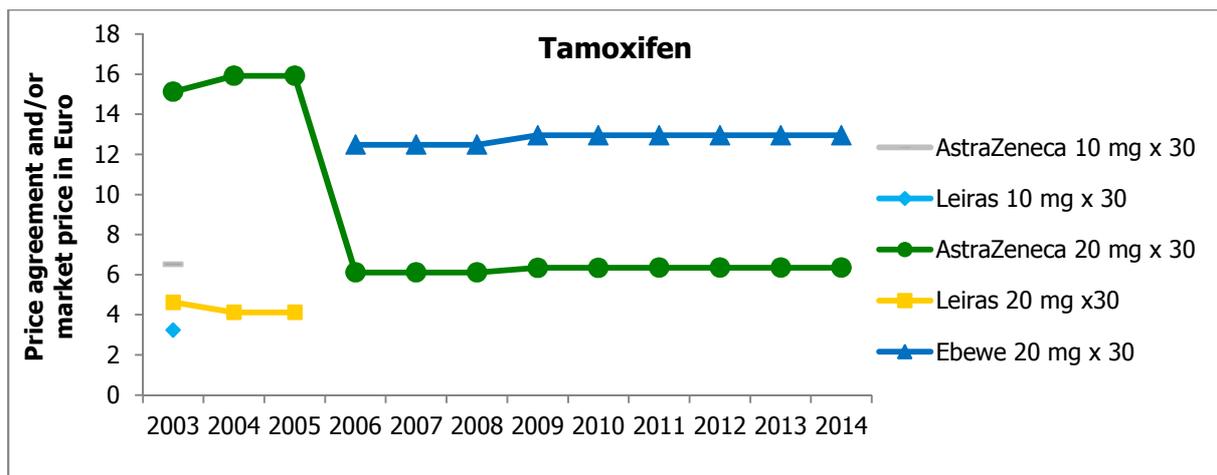


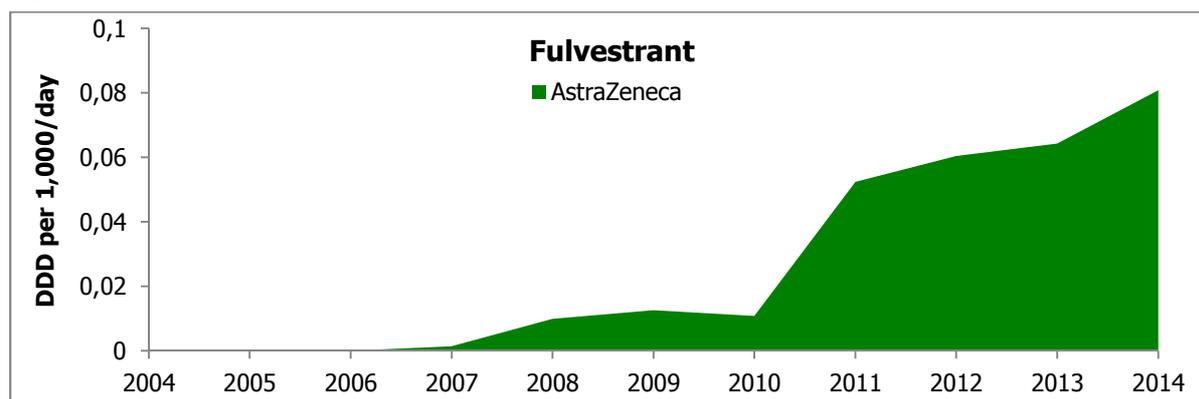
Figure A3.3. Pricing of tamoxifen in Estonia, 2003–2014^a



^a Value-added tax (VAT) was raised from 5% to 9% in 2009.

Toremifene is a centrally authorized medicine but was not consumed between 2006 and 2014. There was no generic fulvestrant on the Estonian market as of December 2014 (Figure A3.4).

Figure A3.4. Consumption of fulvestrant in Estonia, 2004–2014, DDDs

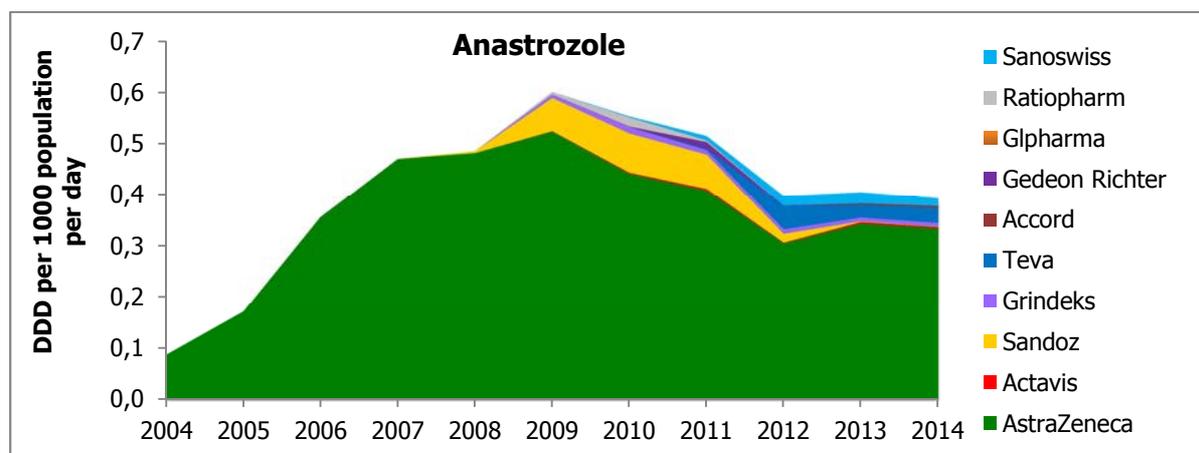


Source: based on data from the EHIF, analysis by the authors.

Generic anastrozole first entered the Estonian market in 2008 and the market share of generic versions reached its highest point in 2012. Since then, the share of generics has been decreasing. In contrast to the limited number of generic versions of tamoxifen, nine generic versions of anastrozole entered the market. The first was made by Sandoz, but had nearly disappeared by 2014. In 2014, the Teva generic version had the highest market share among the generics, but the overall share of generics was less than 20% of total market volume (Figure A3.5).

Figure A3.5. Consumption of different versions of anastrozole in Estonia, 2004–2014. A: DDDs; B: by percentage volume.

A.



B.

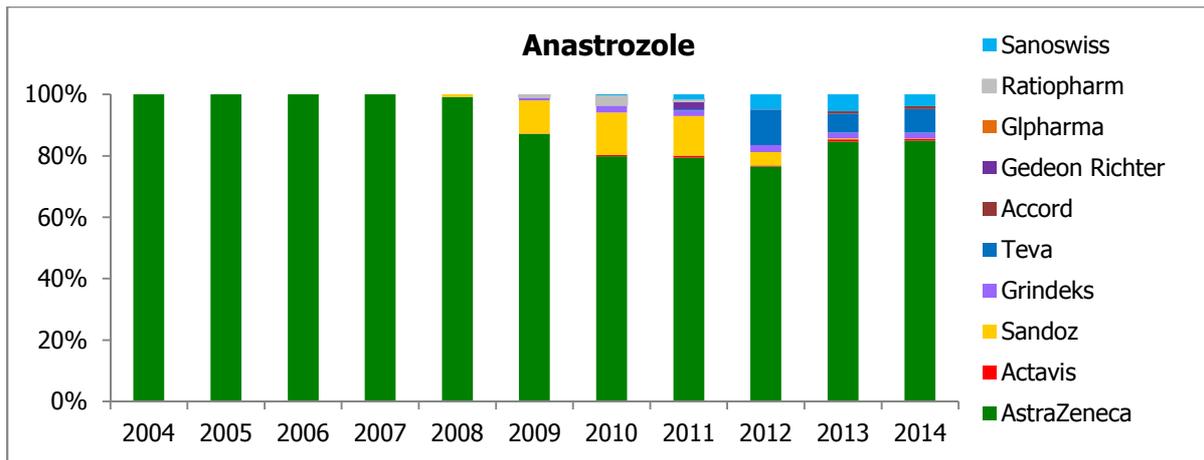
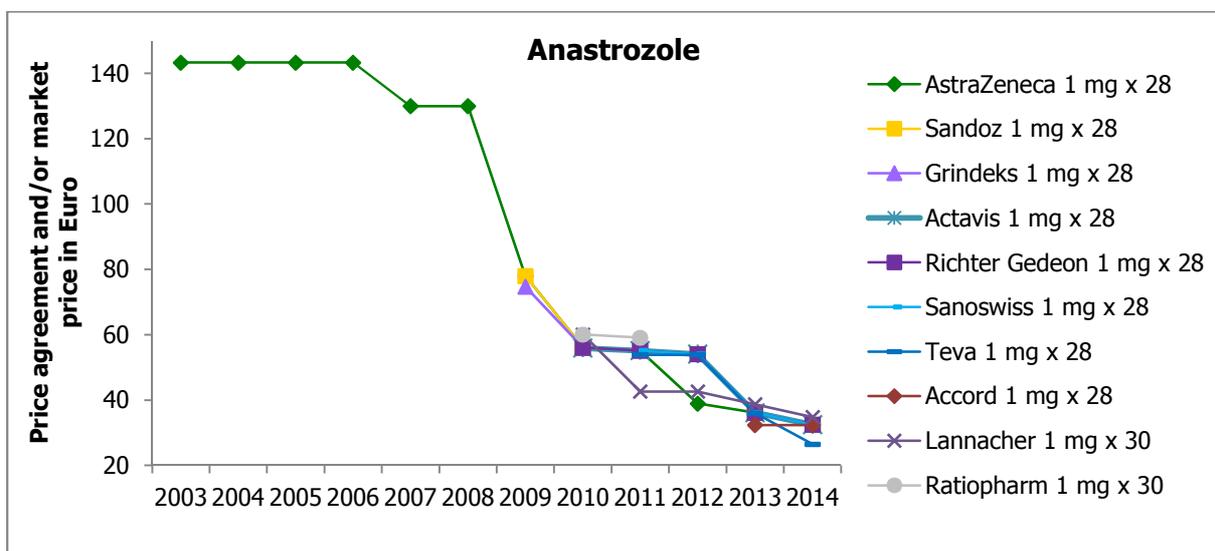


Figure A3.6. Pricing of anastrozole in Estonia, 2003–2014^a

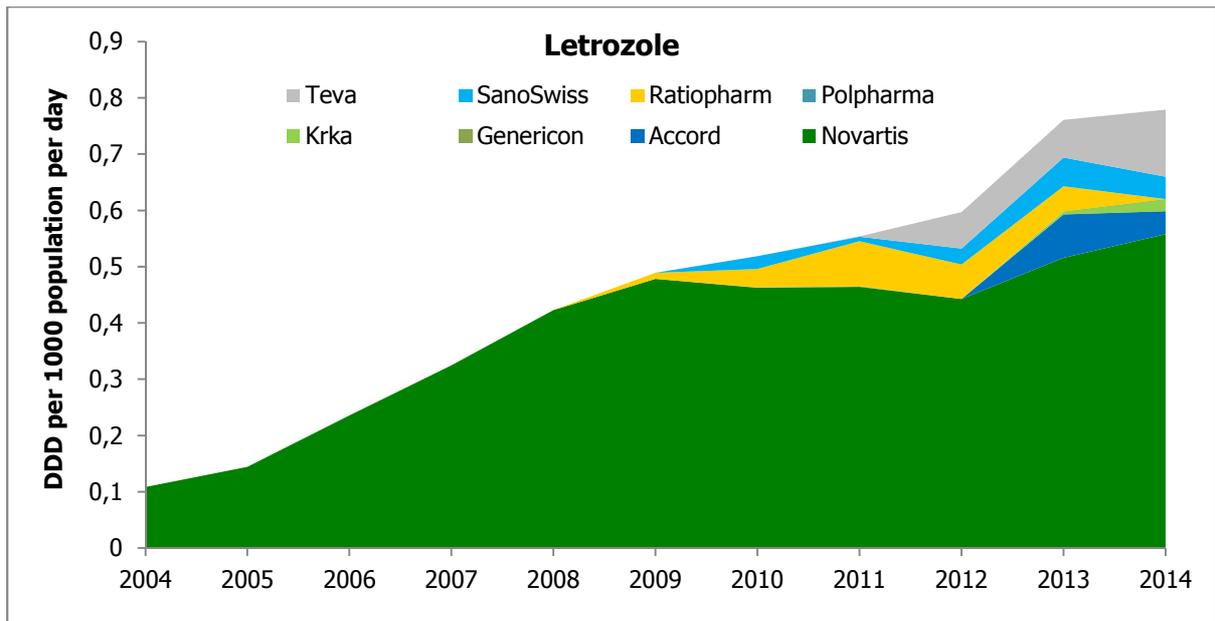


^a VAT was raised from 5% to 9% in 2009

The entry of generic versions of letrozole showed a similar pattern as that of anastrozole. The first generic, produced by Ratiopharm, entered the market in 2009; the following year, three more generics – produced by Genericon, Polpharma and SanoSwiss – entered the market. Ratiopharm had the dominant generic until 2011; it was overtaken by Teva in 2013 and withdrew its version in 2014. Generic penetration was highest in 2013 (Figure A3.7).

Figure A3.7. Consumption of different versions of letrozole in Estonia, 2004–2014. A: DDDs; B: by percentage volume.

A.



B.

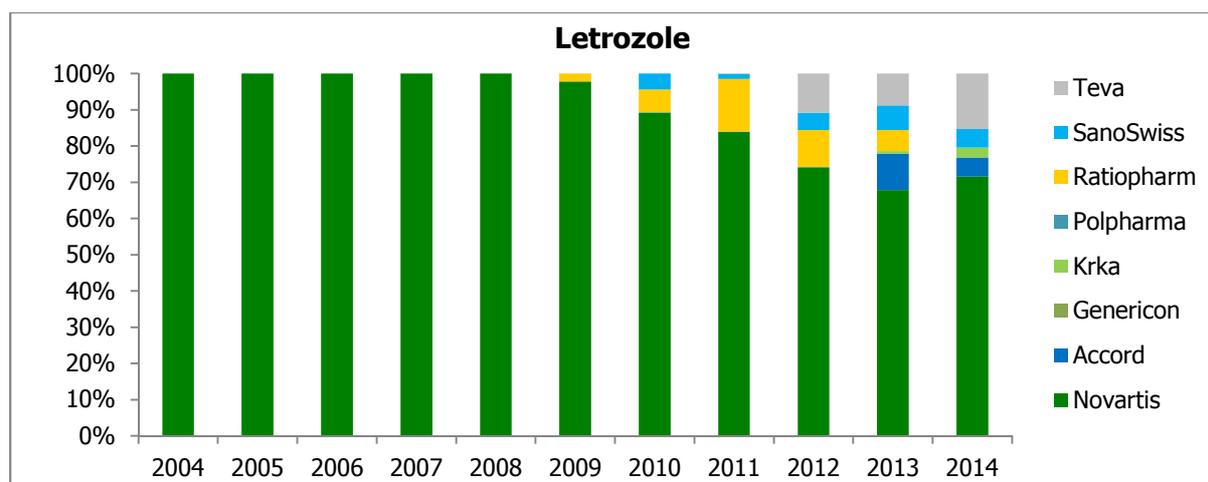
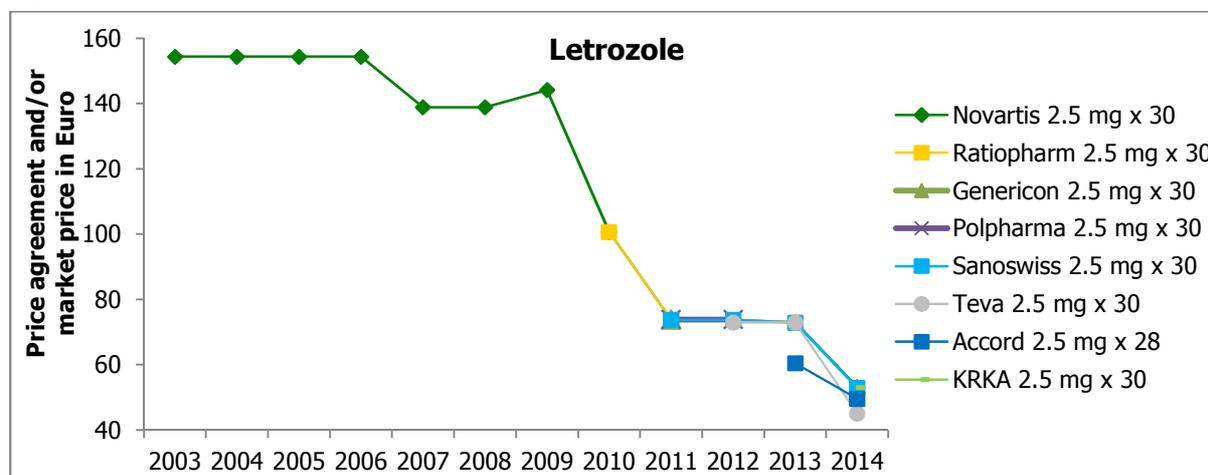


Figure A3.8. Pricing of letrozole in Estonia, 2003–2014^a

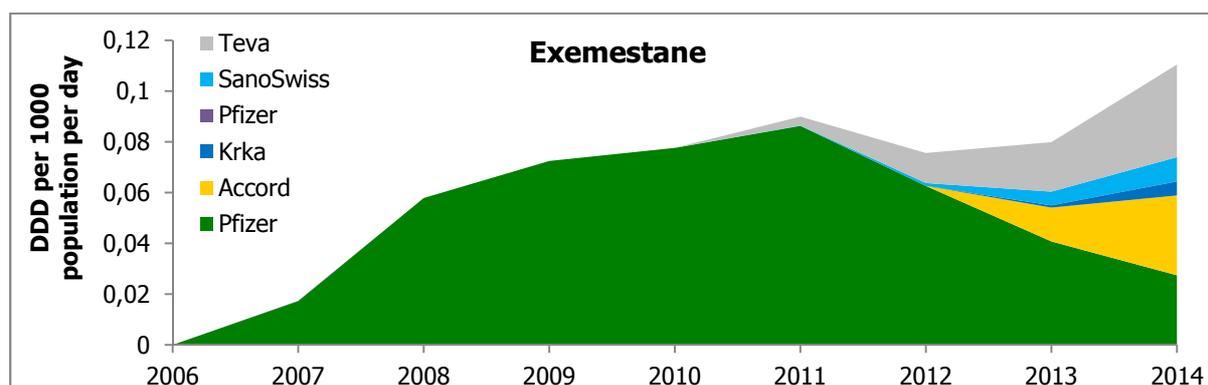


^a VAT was raised from 5% to 9% in 2009.

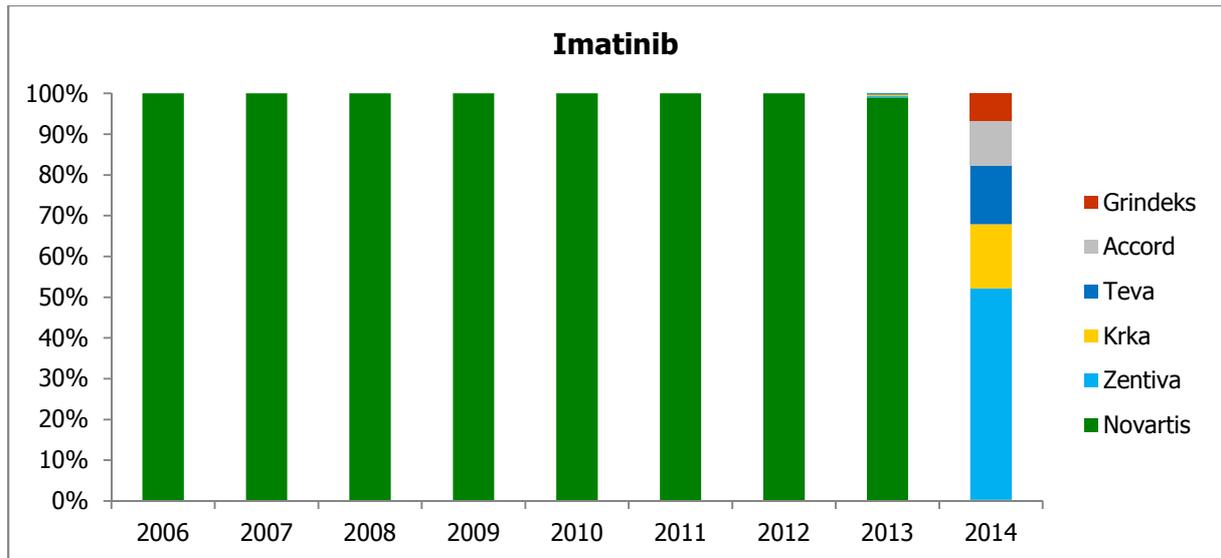
Among endocrine therapies for breast cancer, exemestane is the only active ingredient for which generic versions have overtaken the brand, reaching 75% market share in 2014. As of 2014, this trend showed no signs of reversing. The first generic versions, by Teva and Sanoswiss, entered the market in 2011 followed by Accord and Krka versions two years later. In 2014, Teva dominated the generic market, closely followed by Accord.

Figure A3.9. Consumption of different versions of exemestane in Estonia, 2006–2014. A: DDDs; B: by percentage volume.

A.



B.



Source: based on data from the EHIF, analysis by the authors.

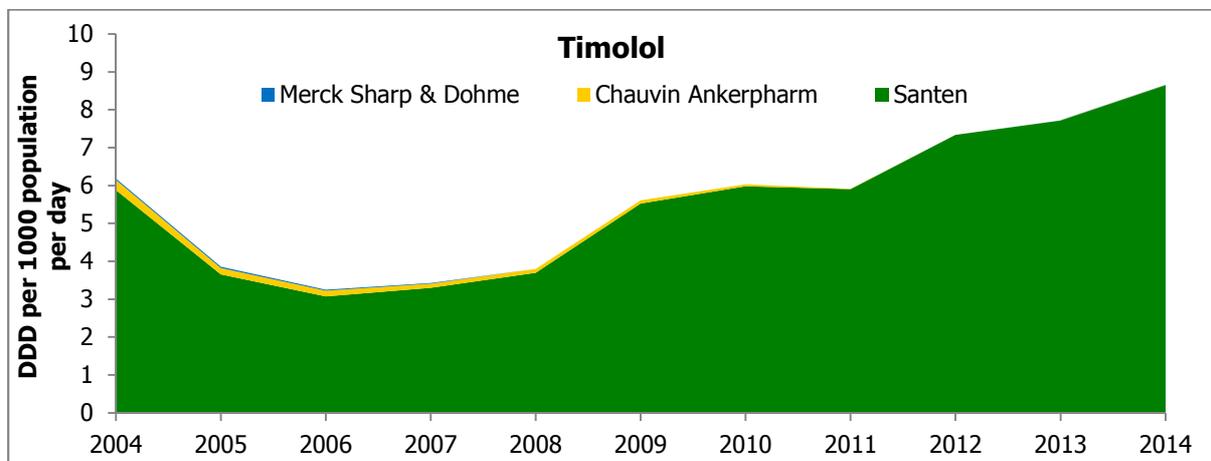
Glaucoma treatments

The following EHIF compensated medicines were used in Estonia for the treatment of glaucoma between 2004 and 2014: acetazolamide, betaxolol, brinzolamide, carbachol, dorzolamide, latanoprost, pilocarpine, pilocarpine + timolol, tafluprost, timolol, timolol + bimatoprost, timolol + brinzolamide, timolol + dorzolamide, timolol + latanoprost, timolol + travoprost, and travoprost.

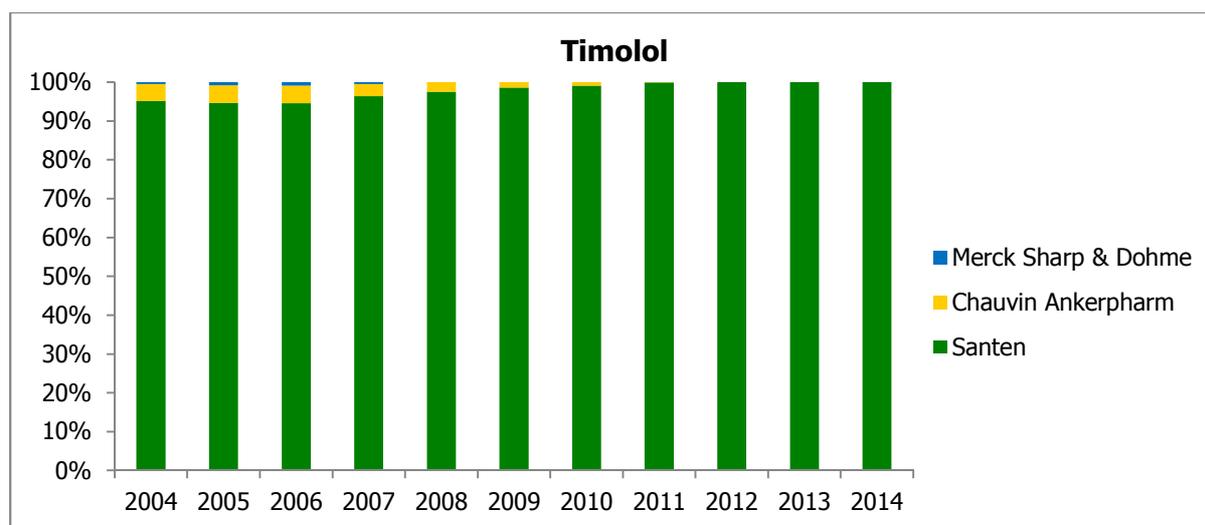
The original manufacturers of the two formulations of timolol were Merck (Timoptic XE gel) and Chauvin Ankerpharm (Arutimol solution). Two generics – Oftan Timolol and Timosan – were made by Santen. Chauvin Ankerpharm obtained a marketing authorization for the solution in February 2000, but disappeared from the market by the end of 2011. Merck obtained authorization for the gel in December 2000, and withdrew it by the end of 2007. As of 2004, the Santen generics were already dominating the market for timolol and, by the end of 2011, both originators had disappeared (Figure A3.11).

Figure A3.11. Consumption of different trade names of timolol in Estonia, 2004-2014. A: DDDs; B: by percentage volume.^a

A.



B.



^a Data for 2004–05 cover only the outpatient sector.

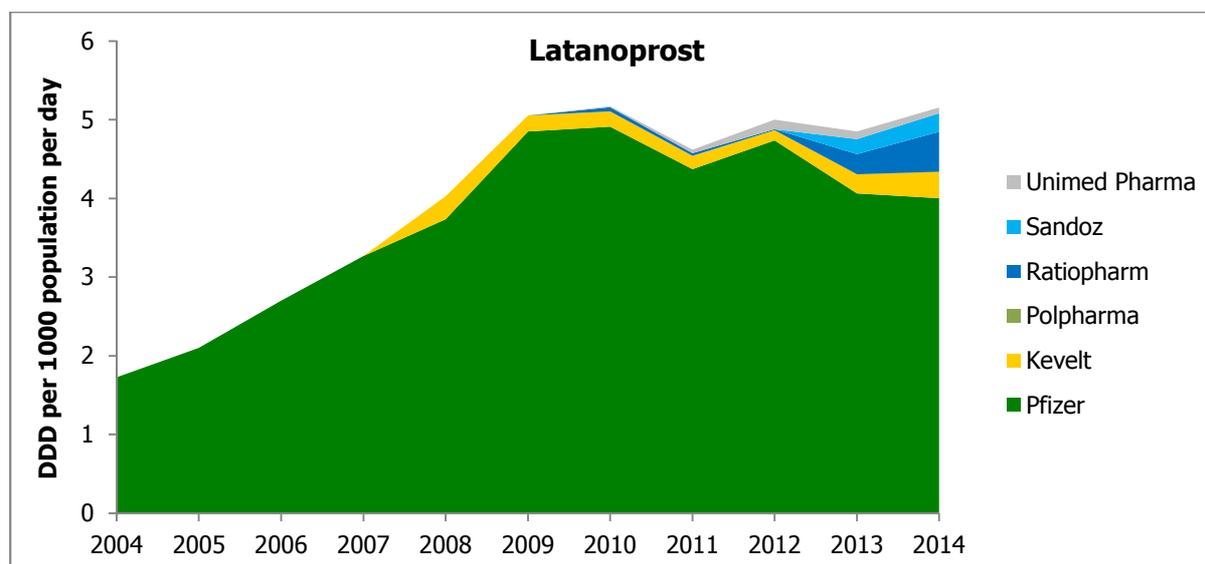
Source: based on data from the EHIF, analysis by the authors.

The first generic version of latanoprost entered the Estonian market in 2008, but the generic market share remained at less than 10% of the total volume up to 2012. From 2013 to 2014, the share of generics increased from 16% to 22%, with Ratiopharm leading the increase (FigureA3.12).

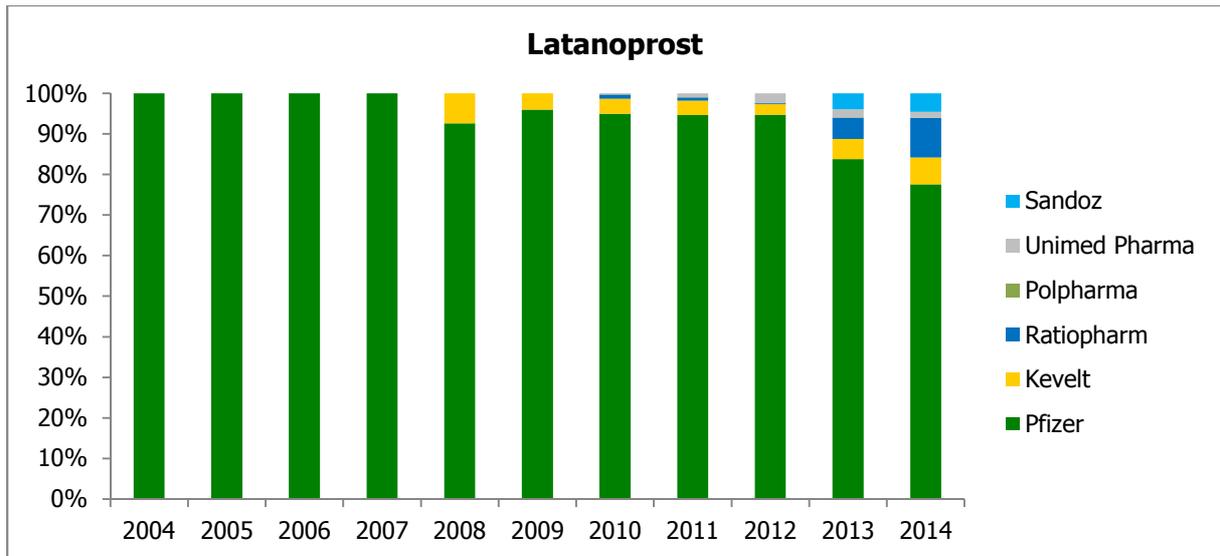
Five other manufacturers had a generic product on the market: Actavis, Dr Gerhard Mann, NTC, Pharmaselect International, and Laboratoires Théa. One generic, Xaloptic made by Polpharma, was withdrawn in October 2014; all other products ever authorized were still present.

Figure A3.12. Consumption of different trade names of latanoprost in Estonia, 2004-2014. A: DDDs; B: by percentage volume.^a

A.



B.

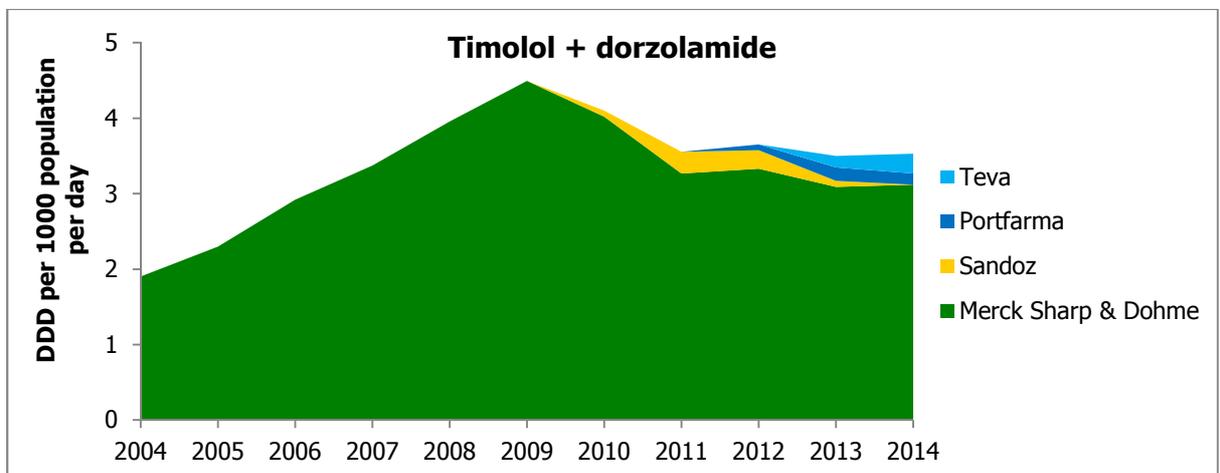


^a Data for 2004–05 cover only the outpatient sector.
 Source: based on data from the EHIF, analysis by the authors.

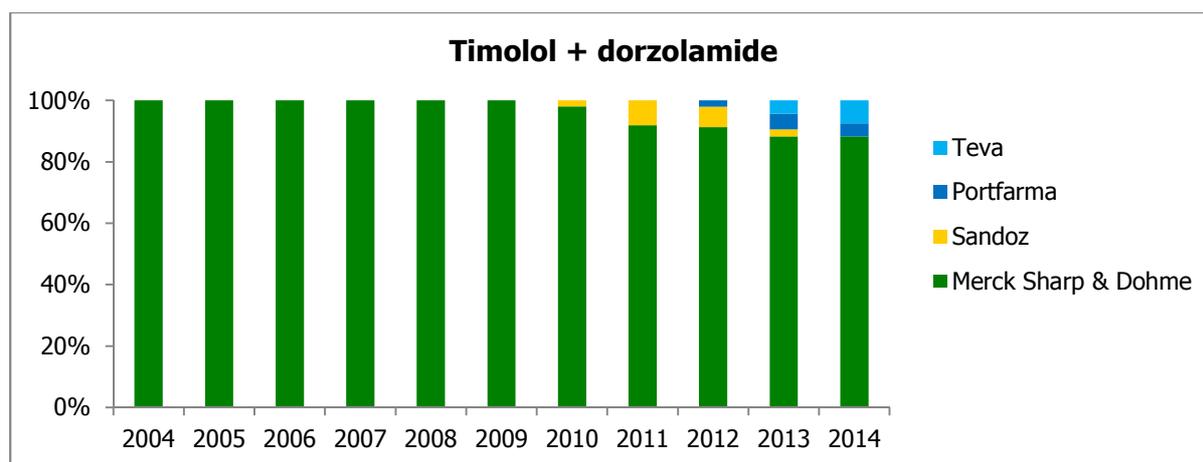
The first generic version of timolol + dorzolamide, made by Sandoz, entered the market in 2010; between 2010 and 2014, the market share of generics increased from 2% to 12%. Yet by 2014, Sandoz had left the market.

Figure A3.13. Consumption of different trade names of timolol + dorzolamide in Estonia, 2004-2014. A: DDDs; B: by percentage volume.

A.



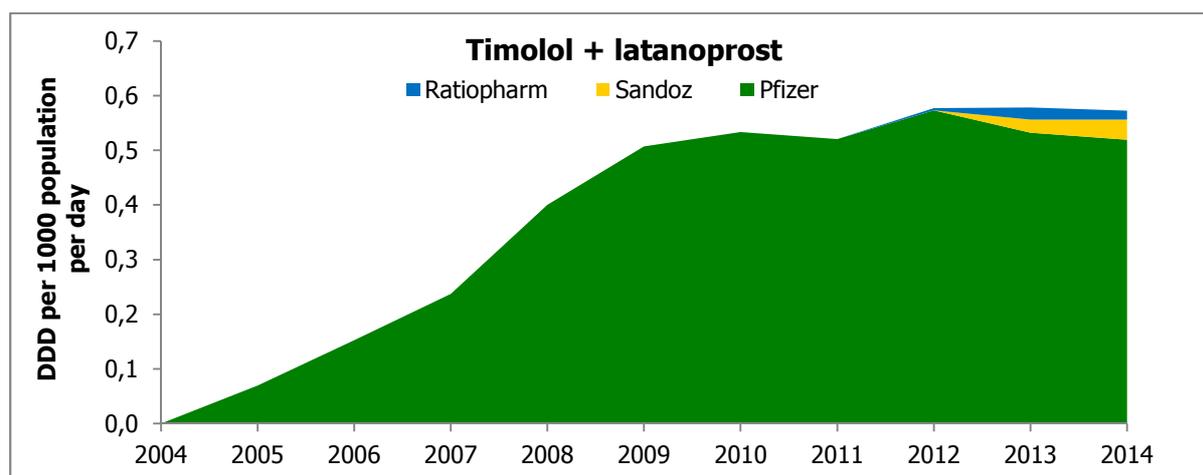
B.



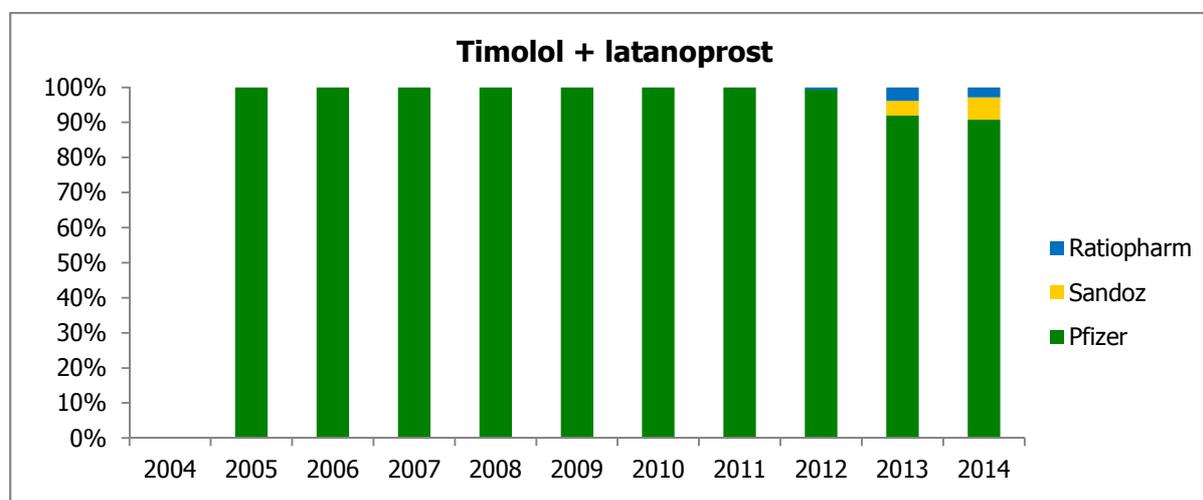
The first generic version of timolol + latanoprost, from Ratiopharm, entered the market in 2012, followed by a Sandoz product in 2014. Sandoz has since taken over Ratiopharm, but their combined market share is still less than 10%.

Figure A3.14. Consumption of different trade names of timolol + latanoprost in Estonia 2004-2014. A: DDDs; B: by percentage volume.

A.



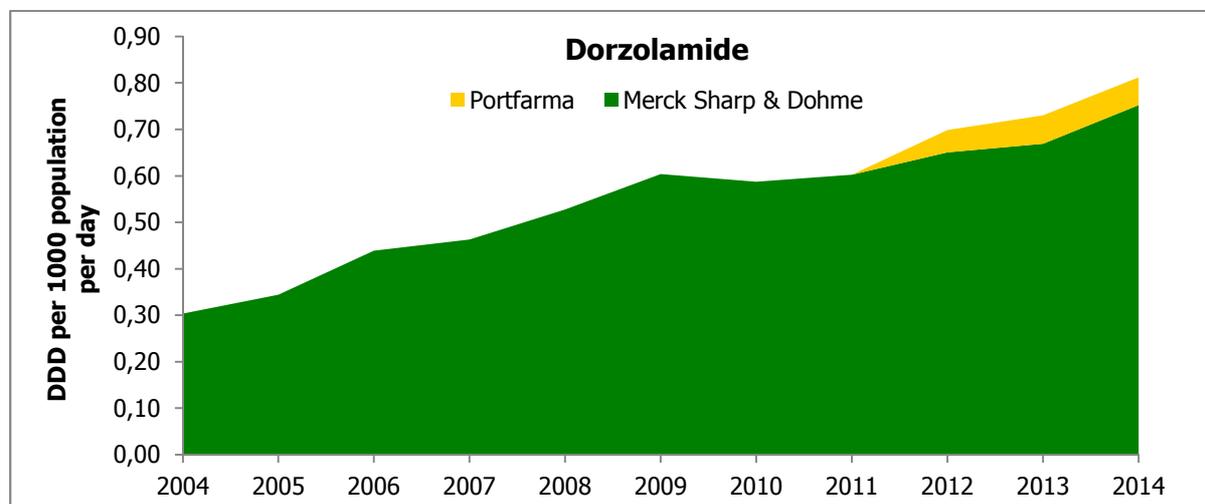
B.



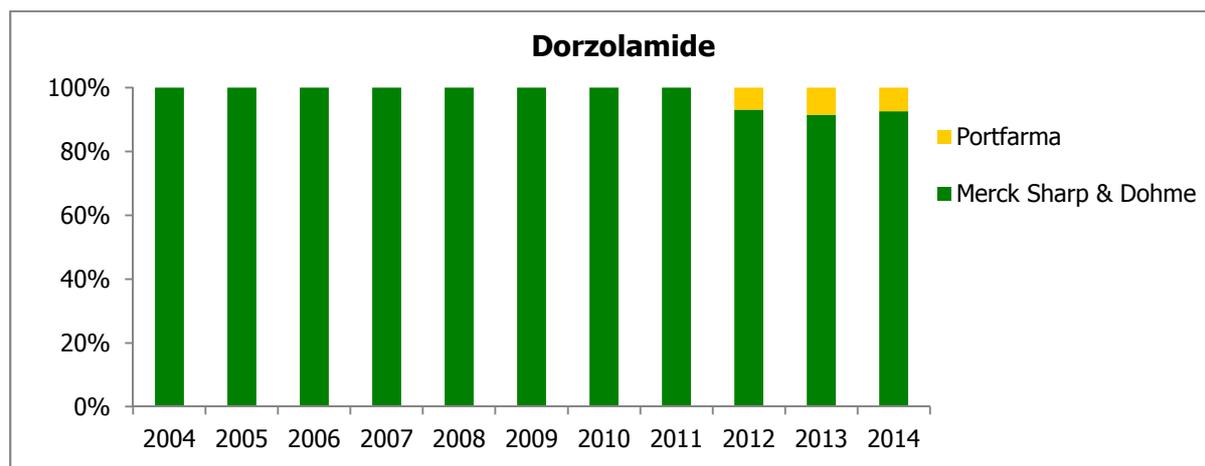
Up to 2014, only one generic version of dorzolamide, made by Portfarma, had entered the Estonian market. Its market share went from 7% in 2012 to 8% in 2013 and back to 7% in 2014.

Figure A3.15. Consumption of different trade names of dorzolamide in Estonia, 2004-2014. A: DDDs; B: by percentage volume.

A.



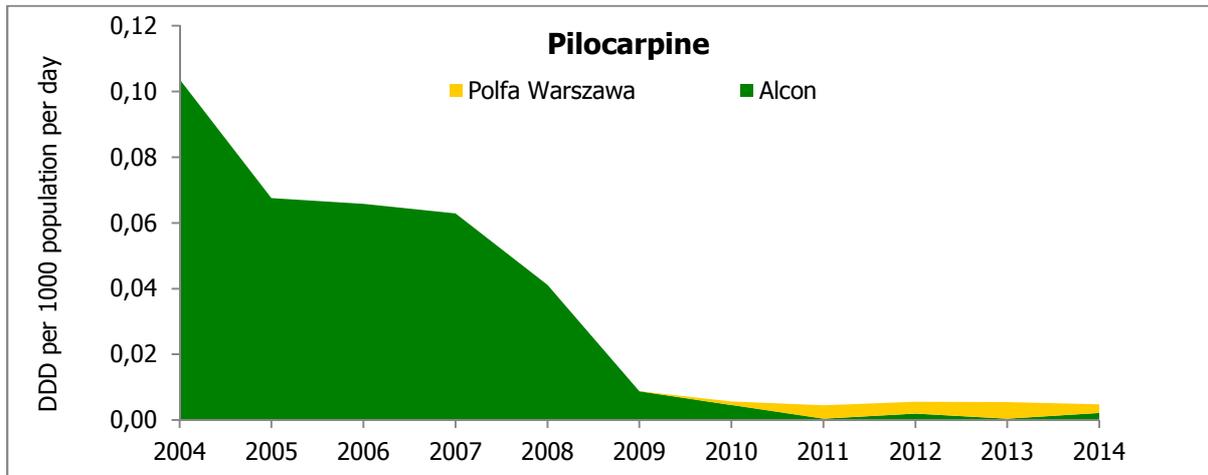
B.



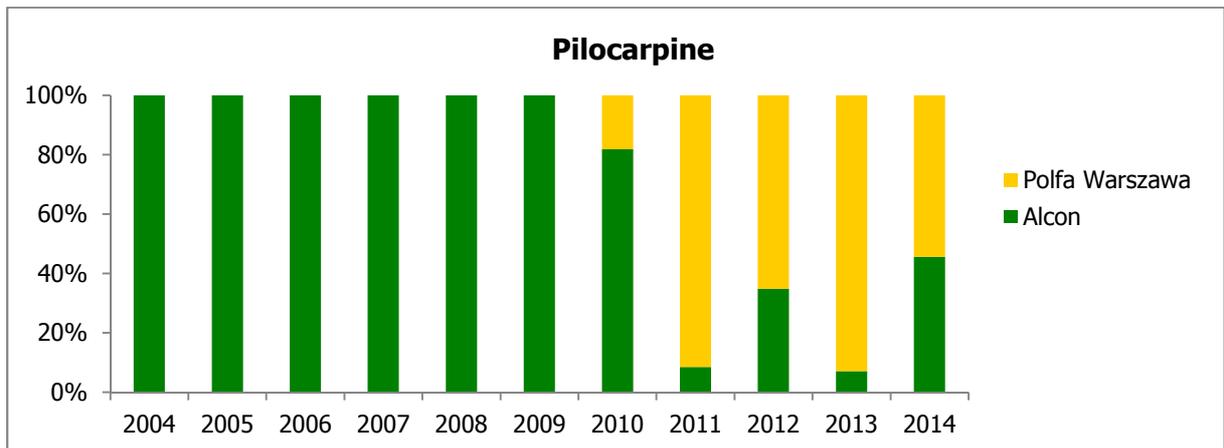
Of all the medicines used for the treatment of glaucoma in Estonia, pilocarpine and timolol are the only medicines with a generic market share higher than 30%. In 2011 and 2013, the generic version of pilocarpine reached a market share of 91% and 93%, respectively. However, the overall consumption of this medicine is very low and has been decreasing over time (Figure A3.16).

Figure A3.16. Consumption of different trade names of pilocarpine in Estonia, 2004-2014. A: DDDs; B: by percentage volume.

A.



B.



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