The climate for innovative medicines in the Republic of Macedonia

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Introduction

The competition between the innovative and generic pharmaceutical companies has intensified in the last decades. Generic medicines have very important role in the development of a sustainable and accessible healthcare system. On the other hand, innovations should be stimulated to maintain and improve the quality of health care. Finding the balance between pharmacotherapy and pharmacoeconomy is one of the key challenges of the pharmaceutical industry and healthcare policies. The inclusion of innovative medicines on the positive lists and the influence of the legislation on medicines price control are important issues for pharmaceutical companies and patients.

The Republic of Macedonia has a limited medicines budget, and its healthcare policies aim to save on medicines supplies. Nevertheless, the country intends to allow the entry and use of innovative medicines, especially for first- and second-line therapy.

The essential part of the model created by the innovative pharmaceutical industry to enable the market exclusivity and increase medicines prices is the system of patent protection. In the Republic of Macedonia, the data, market and new indication exclusivity will be implemented starting from 2017, and the generic medicines can be registered after the patent protection expiry. During the current financial crisis, health authorities decide to promote the use of generic medicines rather than more expensive medicines by originators, faced with increased costs of their national budgets.

The existence of multinational innovative companies is difficult in the circumstances of limited financial means, low GDP, import-oriented small market, absence of national innovative industries and fewer numbers of patients. The probable solutions might be the appropriate price policies that optimise the costs of innovative medicines and their inclusion on the positive list, and guarantee their pharmacoeconomic and therapeutic justification. The legislation and legislative acts in the Republic of Macedonia are constantly modified due to the harmonisation with the European regulation.

Study objective

We aim to describe the circumstances that lead to innovative medicines' entry to the market.

Study methodology

We analyze the legislation in the Republic of Macedonia and other circumstances that influence the innovative medicines' entry to the market.

Overview of the legislation

The main legal acts and by-laws that support the methodology for medicines pricing (including reference pricing), the establishment of the national reimbursement list and the parallel importations have been explained in Table 1.

Table 1: Overview of legal acts and by-laws

Legal acts and by-laws	**Official Gazette / year.**	**Main characteristics related to medicines prices and reimbursement policies**
Law for supplementing and amending the Law on medicinal products and medical devices	88/2010	Instead of given methology about the price formation, new paragraph allows by-laws to treat the matter at technical details level.
Methodology for medicines' single price structure	156/11 45/12	**Referent pricing:** Slovenia, Bulgaria, Netherlands, Poland, UK, France, Croatia, Serbia, Greece, Germany, Turkey and Russia **Maximum wholesale medicines price:** average value of the two lowest comparison wholesale prices from the referent countries **Fees within the wholesale medicine price:** wholesale fees, custom fees, other import fees **Retail margin:** as a percentage of wholesale prices (28%, 25%, 20%, up to 1,200 MKD). **Medicine pricing structure:** suggested retail price – the same or lower price calculated by this methodology **The increase of medicines prices -** pharmacoeconomic study and/or calculations for justification **Brand medicines or innovative medicines** Maximum price – average value of the two lowest wholesale prices of the brand medicine from the same manufacturer in the referent countries **Pharmacoeconomics indicators**
Law for supplementing and amending the Law on medicinal products and medical devices	11/2012	Option given for parallel importation of medicines
Law for supplementing and amending the Health Insurance Law	26/2012	Modification of the mode and the methodology to establish the Health Insurance Fund (HIF) medicines reimbursement list (Positive list):

		Ordinance passed by the Government of the Republic of Macedonia 14 expert committees established by the Government of the Republic of Macedonia according to the international ATC classification, each made from 17 members (14 MDs, 1 MOH representative, 1 clinical pharmacologist or pharmacist) with one year mandate. The committees make the decision based on prior opinion given by an appropriate university clinic.
Ordinance on the mode and methodology to establish the HIF medicines reimbursement list	116/ 2012	Medicines on the list List A – medicines from primary health care, dispensed at the pharmacies contracted by HIF List B - medicines from hospital healthcare Medicines are grouped according to the ATC classification, INN, prescribing regime, indications, application site, dispensing of special group medicines, dispensing and use of medicines according to indications or remarks about the medicines Established procedure on the applications for adding or removing medicines on the list Harmonisation with the HIF financial possibilities. Incorporation of the scientific evidence on drug efficacy, pharmacotherapeutic and pharmacoeconomic indicators and established medicines price. Incorporation of the pharmacoeconomic and financial analysis, wholesale prices according to DDD and info on medicines inclusion on the positive lists in the EU countries or other with comparative economic systems. List revision at least annually
Health Insurance Fund (HIF) medicines reimbursement list (Positive list)	81/2012 revised text	Number of amendments and additions – medicines dispensed according to the INN and ATC classification – preferences towards generic medicines – small number of innovative medicines – Listed indications for reimbursement – 377 medicines by generic name on the primary positive list – 343 medicines by generic name on the hospital positive list
Rulebook on the criteria and procedures to establish medicines reference prices	158/ 2009 138/ 2010	Referent countries: Slovenia, Croatia, Bulgaria, Serbia – Harmonisation of the refence price with the purchasing power parity coefficient – The price of medicine with no generic competitor cannot be higher than 10% of the average comparison price – The price of medicine with generic competitor cannot be higher than 79,23% of the average comparison price – The option to include the therapeutic equivalent for

		medicines with the same efficiency/safety – determination of pharmacological therapeutic groups – Reference prices are established on 10 January each year.

Discussion

The Law on medicinal products and medical devices from 2007 has been modified to include the reference pricing methodology in 2010 and the parallel importation in 2013 (Table 1). The by-laws have further explained the medicines pricing and the registration procedure (including the 5% VAT). The reference countries for establishing the unique medicines prices include not only the EU countries, but also Serbia, Turkey and the Russian Federation (Table 1). Some of them differ significantly from Macedonia in terms of the size of the country, its medicines market, or financial parameters. The reference pricing methodology sets very low unique medicines prices, and only medicines of special interest can be up to 20% higher than the average wholesale prices in the referent countries (Table 1). It lowers the companies' profit, threatens their financial viability, and decreases further the small interest of innovative companies for the Macedonian market. Some of them have been closing their representative offices in the country.

As illustrated in Table 1, the reimbursement of medicines is regulated by the Health Insurance Law and the Ordinance 116/2012, while the modified methodology for the list has been added to the law in 2012. The establishment of expert committees in charge fof the positive list is underway. However, the complexity of the procedure delays and hampers the process of adding new medicines on the list.

According to the Health Insurance Law, the insured citizens are entitled to use reimbursed medicines on prescriptions, while these medicines are dispensed by pharmacies contracted by the HIF (Table 1). The list of expensive medicines are not included in pharmacies' monthly quotas, and are determined by HIF decisions.

The inclusion procedures for the reimbursement list were defined with the 2012 Ordinance. The additions and deletions on the list have to be based on evidence on medicines efficacy, pharmacotherapeutic and pharmacoeconomic indicators, and in line with the HIF financial possibilities. It also requires data on drug inclusion on the reimbursement lists in the EU or countries in the region. .

The prescribing of reimbursed medicines by generic name (INN) has been implemented in 2003 as part of the HIF agreement with the MDs from primary health care. The generic

prescribing has been one of the successful methodologies to reduce the medicines costs, but has also a negative impact on the brand medicines supply and reduces prescribers and patients' choice. The HIF negotiates with the pharmaceutical companies the price alignment of brand medicines and pre-determined reference prices of generic medicines to achieve lower prices. The new methodology for unique medicines prices and the market competition have resulted in savings in the national drug budget. These savings can be used to introduce the required innovative medicines on the market.

The medicines from the hospital positive list are provided through the healthcare institutions, and their prices have no impact on the patients, but on the limited hospital budgets.

The national medicines budget has currently reached 154 million Euros, with 40% for the reimbursed medicines, and 60% for commercial ones. Around 3510 medicines are registered in the country, which includes 2623 generic (75%), 735 brand (21%) and 152 innovative medicines (4%). The small number of registered innovative and brand medicines is a result of the generic prescribing policies, the unique medicines price methodology, the reference pricing for reimbursed medicines, the delays, and the strict inclusion rules for the positive list. The reimbursement policies are in more favour of generic compared innovative medicines. The reference pricing has reduced the prices of most medicines on the reimbursement list, but only few innovative medicines can decrease their prices. The mandatory generic prescribing and the pharmacies' obligation to offer the reference priced medicine reduce the opportunity to sell the brand medicines.

The national health authorities consider the positive list to be made according to the WHO recommendations for the selection of essential medicines, meeting the population clinical needs for most common diseases in the country and according to the financial resources available. The last revision of the list has been done based on the HIF Steering Committee decision and opinions of the expert committees appointed by the Minister of Health, but whose responsibilities ceased with the amendments to the Health Insurance Law in 2012. During the active period of this committee (2007-2012) the biggest pressure for inclusion on the list has been related to the medicines listed in Table 2.

Table 2: Requests for inclusion of innovative medicines on the reimbursement list (2007-2012)

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ATC code	INN	Name of the medicine	Manufacturer	Registration date
L01XA03	oxaliplatin	Eloxatin Oksaliplatin	Aventis farma Sanofi-Aventis Cipla Ltd. EBEWE Pharma PLIVA LACHEMA a.s.	13.05.2010 30.06.2009 29.03.2012 30.06.2009
L01XC07	bevacizumab	Avastin	Hoffman la Roche	28.09.2010
L01XE01	imatinib	Glivec Anzovip Imakrebin Plivatinib	NOVARTIS Pharma ZDRAVLJE A.D. - Лесковац, REMEDICA Ltd - Лимасол, Кипар PLIVA Hrvatska	25.03.2011 25.12.2012 24.01.2013 29.11.2012
L01XE03	erlotinib	Tarceva	Hoffman la Roche	28.10.2010
L01XC04	alemtuzimab	Mabcampath	Boehringer ingelheim	28.10.2010
B01AX06	rivaroxaban	Xarleto	BAYER SCHERING PHARMA AG	30.12.2008

Only Imatinib was put on the positive list (Official 62/2011), including three more medicines with the same generic name later on. Other listed medicines have been rejected on the justification for limited national financial means and the existence of therapeutic alternatives. All these medicines have all been registered in the country, but their presence on the Macedonian market depends largely on their inclusion on the reimbursement list. Since 2012, the 14 expert committees have not been appointed yet, so there have been no new applications for inclusion on the list.

The innovative companies reduce the medicines prices according to the methodology for unique medicines prices and direct negotiations with the HIF. They estimate that this has led to the approximate savings of 20 million Euros, which shall be used to include new innovative medicines on the reimbursement list when they have the pharmacoeconomic justifications. Additional savings can also be generated by rationalising the positive list, drug use in the hospitals and reference prices. The more frequent revision of the positive list (i.e. quarterly) can result in the elimination of obsolete medicines and inclusion of innovative medicines.

The financial existence of the innovative companies in the Republic of Macedonia is of strategic importance for the country in terms of data provision on innovative medicines, presence on the market and post-marketing surveillance.

The parallel import from 2012 will improve the market offer, but will have a negative impact on the financial sustainability of the innovative companies' representation in Macedonia.

Conclusion and recommendations

National regulations were put in place to accelerate the access to innovative medicines. Simultaneous legal changes and drug pricing policies were designed to support the generic market rather than innovations, and control drug budget. This illustrates the national dilemma of how to improve access to innovative medicines beneficial for patient health with restrictive budget.

- The Republic of Macedonia has limited drug budget, so its policies are directed towards saving of the resources for drug supplies.
- The country aims to allow the market entrance of innovative medicines and their use, especially for first- and second-line treatments in line with its financial possibilities.
- In recent years, the regulation has been modified to facilitate the market entrance for innovative medicines. However, frequent modifications and adjustments according to all interested parties have delayed the process of their efficient implementation
- The generic prescribing and reference pricing have a negative impact on brand medicines and limit the choice of prescribers and patients, but save the budget resources that can be used to include innovative medicines on the market and the reimbursement list.
- The parallel importation is benefiacial to the market offer, competition and medicines prices, but hampers the financial sustainability of the innovative companies' representative offices.
- The discontinued legal procedured in the last year and the complicated procedures delay its completion and the inclusion of innovative medicines on the positive list.
- The reduction of medicines prices using the methodology of unique prices and reference prices for reimbursed medicines can free some resources to be used to include new medicines in health care, but lower prices decrease the innovative companies' interest to enter the Macedonian market.

- Given the limited and insufficient drug budget, savings can be made by rationalising the positive list, use of medicines in hospital and introduction of pharmacoeconomic aspects in practice, which can be used to include new medicines for patient care.
- Still, the inclusion of expensive innovative medicines should be based on scientific evidence on drug efficiency (first- and second-line therapies), pharmacotherapeutic and pharmacoeconomic indicators and HIF financial possibilities.
- The presence of innovative medicines on the Macedonian market and their inclusion on the positive list shall be done according to the experience in the EU and countries in the region with comparative economic systems.

References:

1. Law for supplementing and amending the Law on medicinal products and medical devices. Official Gazette 88/2010
2. Methodology for medicines' single price structure. Official Gazette 156/2011, 45/2012
3. Law for supplementing and amending the Law on medicinal products and medical devices. Official Gazette 11/2012
4. Law for supplementing and amending the Health Insurance Law. Official Gazette 26/2012
5. Ordinance on the mode and methodology to establish the HIF medicines reimbursement list. Official Gazette 116/2012
6. Health Insurance Fund (HIF) medicines reimbursement list (Positive list). Official Gazette 81/2012 revised text
7. Rulebook on the criteria and procedures to establish medicines reference prices. Official Gazette 158/ 2009 and 138/ 2010.