Health technology assessment of biotechnology medicines with focus on hospital pharmacy

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Abstract *- The study aims to present a general overview of the process of HTA for biotechnology medicines in Bulgaria with special emphasis on hospital practice.*
It is a regulatory and desktop analysis. We studied the current regulation for HTA of new medicines in Bulgaria for special requirements towards biotechnology medicines for hospital use. A review of the scientific literature on the topic was also undertaken for articles from Bulgarian authors in the field.
HTA in the Bulgarian regulatory practice was introduced in 2015 with changes in the Drug Law. The law necessitated that the National Pricing and Reimbursement Council had to perform a HTA of new medicines for the purposes of their inclusion into the Positive Drug List. Our study identified 30 articles, and out of them 17 meeting the inclusion criteria. Those studies could be separated in three therapeutic areas – diabetes, oncology, rare diseases therapy. In the above mentioned areas, newly introduced biotechnology medicines prevail and part of them are originator, others are generic medicines.
The process of HTA did not differ between synthetic or biotechnology medicines in Bulgaria. Listing and inclusion into the positive drug list is separated between medicines for ambulatory and hospital settings. Hospital pharmacies should develop rules for internal evaluation of the new technologies from the point of view of the hospital budget.

Keywords *- health technology assessment, biotechnology medicines, hospital practice, hospital pharmacy*

Introduction

Health technology assessment (HTA) is a relatively new scientific field developed to aid the decision making process in health care. In its essence, HTA is a process of systematic evaluation of possibilities and results of new health technologies, which focus on the direct and indirect effects of this new technology, as well as its unexpected consequences [1]. It is a multidisciplinary process of data and evidences collection of medical, social, and ethical aspects of new technology utilization, in a robust, scientifically systematic, transparent, and objective way [2]. Despite of its regulatory goals the HTA should always be based on robust scientific methods and evaluate the efficacy, effectiveness in real practice, safety and cost of new technology and their potential financial burden on the budget [3, 4, 5].

Health technologies could be preventive or prophylactic measures, rehabilitation services, medicines, medical devices, medical and surgical procedures, as well as new health care programs [6]. Although lots of new technologies are constantly being developed, the main focus of HTA is still on medicines mostly due to the established regulatory rules for their efficacy, safety and prices control [7].

Many biotechnologically derived medicines have recently been placed on the market as new technologies posing financial challenges in front of hospital pharmacies mostly because of their high prices and constantly rising prescribing [8]. This, to some extent, burdens hospital budgets and therefore assessment of their benefits are necessary.

There is a lack of publications which focus on the influence of HTA on the hospital budgets especially for newly derived biotechnology medicines, prompting our interest on the subject.

The current study aims to present a general overview of the process of HTA for biotechnology medicines in Bulgaria with special emphasis on hospital practice.

We try to explore whether there are any differences between the assessment of biotechnology products and regular medicines for use in a hospital pharmacy and what could their impact on hospital budgets be..

I. MATERIALS AND METHODS

The study is a regulatory and desktop analysis. We studied the current regulation for HTA of new medicines in Bulgaria and analysed whether there are special requirements towards biotechnology medicines for hospital use.

A review of the scientific literature on the topic was undertaken to assess the available articles from Bulgarian authors in the field and their probable utilization for hospital settings.

Scientific articles were derived from international and national databases such as PubMed, Google Scholar, and Scopus. Key words for literature search

consisted of: biotechnology medicines, Bulgaria, regulatory requirements, hospital pharmacies.

The inclusion criteria were Bulgarian authors, biotechnology medicines assessment, and hospital pharmacy application. The exclusion criteria were articles from non-referenced journals.

No language restrictions were applied..

II. RESULTS AND DISCUSSION

A. Regulatory analysis

HTA in the Bulgarian regulatory practice was introduced in 2015 with changes in the Law for medicinal products in human medicine [9]. The law necessitated that the National Public health institute and later the National Pricing and Reimbursement Council (NPRC) had to perform a HTA of new medicines for the purposes of their inclusion into the Positive Drug List (PDL). A supplement to the Regulation defines the procedural details regarding the conditions, rules, and order for registration of medicines and their prices (Chapter 6) [10]. HTA is not required for essentially similar medicines, and medicines with well-established use.

The regulation requires new medicines to have a positive evaluation from at least one national HTA Regulatory agency like NICE (UK), TLV (Sweden), HAS (France), or IQWICK (Germany). The evaluation is part of the procedure for new medicines inclusion into the PDL and contains information about the clinical and pharmacoeconomic characteristics of the new medicine. Marketing authorization holders apply for evaluation through a dossier structured in the following parts:

- health problem analysis;
- comparative analysis of therapeutic efficacy, safety, and effectiveness of the medicinal product with available alternatives in the therapeutic practice;
- pharmacoeconomic analysis of the cost and consequences of new medicines application in the health care practice;
- Budget impact analysis.

National pricing and reimbursement council evaluates the dossier according to the following criteria:

- availability or lack of alternative disease therapy for which the new medicine if recommended;
- availability or lack of alternative medicines for the disease therapy;
- efficacy and therapeutic effectiveness of the new technology – evaluation of the therapeutic benefits, life expectancy increase, quality of life improvement, complications decrease, or other benefits;
- number of potential patients;
- safety of medicinal product – frequency and severity of adverse drug reactions (ADR), need for additional therapeutic measures application for ADR prevention or treatment;
- pharmacoeconomic characteristics – cost of therapy with the new medicine, comparison with the cost of therapy with already available medicines, cost-effectiveness ratio, economic evaluation of additional benefits;
- benefits of the new technology in terms of life years gained (LYG), quality adjusted life years (QALY), long term benefits;
- budget impact analysis of the new technology and expected number of patients;
- public expenditures during the next 5 years;
- ethical considerations in case of specific group of diseases.

Medicinal products with insufficient evidences for their therapeutic effect are a subject of therapeutic effect monitoring after their inclusion into the PDL. HTA is also requested in case of new indication claims of already included medicines.

The NPRC is employing an external experts group of clinicians, pharmacists, economists and lawyers to assess the dossier supplied by the marketing authorization holder (MAH) after which, the assessment is discussed with the representatives of the National Health Insurance Fund (NHIF) and Ministry of health (MoH) in order to finalize the decision for inclusion into the PDL. After inclusion into the PDL the medicines begin being reimbursed with public funds for ambulatory or inpatients. Annex 2 of the PDL contains all medicines that could be supplied to hospital pharmacies and are a subject of reimbursement.

There are no special requirements in case of evaluation of biotechnology medicines that differ from that of other medicines requirements. The biosimilar medicines are authorized for reimbursement without HTA if the same INN is already included into the PDL. Lots of biosimilar medicines are included into the PDL as infliximab, erythropoietin, growth hormones, colony stimulating factors, biotechnological for inflammatory and autoimmune diseases, insulins etc.

B. Publications analysis

Our study identified 30 articles, and out of them 17 meeting the inclusion criteria were analysed. Those studies could be separated in three therapeutic areas – diabetes therapy, oncology therapy, rare diseases therapy. In the above mentioned therapeutic areas, newly introduced biotechnology medicines prevail and part of them are originator, others are generic medicines with expired patents. We also identified regulatory articles discussing the prices or regulation of the biological or biosimilar access to market [11, 12, 13]. They revealed that many differences exist in the approach to biotechnologies access to market between countries, which has had a variable effect on the level of access to therapy for patients. No unified European pricing and reimbursement policy exists. Vaccines as biotechnology products were also a subject of evaluation and authors found that the vaccination against hepatitis A of one-year-old children would be cost effective to the health care system in the years with an epidemiologic outbreak.

National screening programs were recommended for earlier diagnosis of hepatitis C infection, because the screening of the birth-cohort type (aged 39–64 and born before the blood testing became available) provides benefits compared to the current practice of symptomatic testing [14, 15] New diabetic therapies like insulin liraglutide, degludec, exenatide were found to be cost-effective for the Bulgarian health care settings after modelling the progression of the diseases [16, 17, 18]. Improved quality of diabetes control not only decreases the complications, but also their cost [19]. Entrance of biologicals in diabetes therapy increases the life expectancy of diabetic patients. [20]

Oncology diseases pose a huge burden on the health care system and introduction of tyrosine kinase inhibitors (TKI) lead to a constant decrease in the number of affected patients by approximately 3000 people from 2015 to 2016 and at the same time improves their quality of life [21, 22]. The chronic myeloid leukemia as one of the rare hematological malignancies according to the European Orphan Drug Regulation 141/2000 is nowadays treated with first generation TKI. An alternative for patients who have become resistant to this drug include either increasing the imatinib dose or using second-generation tyrosine kinase inhibitors—dasatinib or nilotinib [23].

In the area of other rare disease therapy we performed an overview of articles assessing the access to the national market [24]. Authors remarked that although pharmacoeconomic requirements about orphan medicinal products (OMPs) inclusion in the positive drug list (PDL) in Bulgaria are implemented, there is a need for more specific criteria. The OMPs included in the PDL in 2017 represented 22.34% of all OMPs in the European Union. For example patient with acromegaly are only 191 in the whole country but the level of comorbidities is very high as more than 95% suffered from at least one concomitant disease [25]. Therefore national policy on the rare diseases therapy could improve access to new biotechnology therapy. Hemophilia, as the other deadly, inherited rare disease is nowadays treated with modern coagulation factors, which are more effective but also more expensive. If the therapy is performed not on demand but in a prophylactic manner many bleeding incidents could be prevented and expensive procedures could be saved [26]. Hemophilic patients require inhibitors and new biotechnology bypassing agents are a cost-effective option for their therapy [27].

III. DISCUSSION

In this study we tried to analyze the impact of HTA in Bulgaria on the access to biotechnology medicines with special emphasis on hospital pharmacy practice. All articles exploring the biotechnology medicines from the point of view of the NCPR proved that they are cost-effective in terms of providing more benefits than cost for the health care system. The process of HTA is highly detailed and we consider provided evidences as robust. The question remains for the cost and particularly whether hospital pharmacies can afford it.

The cost of the therapy of rare diseases and oncology medicines is directly reimbursed by the National Health Insurance fund (NHIF) therefore such medicines would not pose a burden on hospital budgets. But for other medicines like for example antirheumatics it is part of the cost of the whole therapeutic process outlined by guidelines [28].

Studies show that HTA agencies worldwide have different requirements towards the evaluation of the biotechnological products for rare diseases. All European Union countries have developed and implemented pharmacoeconomic guidelines with or without some specific reimbursement requirements for orphan medicinal products, necessitating the implementation of cost-effectiveness analysis, cost-utility analysis, Markov models, meta-analysis etc. The number of reimbursed biotechnologicals for rare diseases differs at national level in comparison with the issued marketing authorizations by European Medicines Agency (EMA) [29]. European patients have unequal access to biotechnology medicines for rare diseases and this could also ruin the national and hospitals budgets especially if they have to transfer the patient abroad for therapy.

The other question that needs to be discussed is the access to biosimilars [30]. They decrease the prices of originators, but the physicians' reluctance to prescribe them is very high. This is partly due to the fact that the principle of essential similarity is not valid for biosimilars and originators due to differences in the production processes. During the HTA process some key questions exist that need to be answered. The first one refers to the effectiveness evidences and establishment of their equivalence during the process of evaluation. It is necessary to provide evidences that originator and biosimilar were compared during the randomized clinical trials [31]. If they were compared and no differences were found we could consider them as essentially similar. Despite the lack of differences in the effectiveness there could be differences in the safety of the biosimilar. Therefore, safety profile also needs to be evaluated. Hospital pharmacists should have information about all those evidences in order to best advise physicians on changes to patients' medicines.

Regarding the cost issue, the NHIF is currently reimbursing medicines at the level of the lowest priced molecule with the same INN. This puts a burden on patients by having them co-pay for the more expensive originator molecules, which could lead to their transfer to a less costly biosimilar alternative. This sometimes could increase certain risks in the whole therapeutic process, especially for transplant patients [32]..

IV. CONCLUSIONS

The process of HTA did not differ between synthetic or biotechnology medicines in Bulgaria. Listing and inclusion into the positive drug list is separated between medicines for ambulatory and hospital settings. There is need for evaluation especially if the medicines are for oncology, rare diseases or diabetic patients due to their high prices. Hospital pharmacies should also develop rules for internal evaluation of the new technologies from the point of view of the hospital budget.

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