

FIRST MACEDONIAN AND FOURTH ADRIATIC CONGRESS ON PHARMACOECONOMICS AND OUTCOMES RESEARCH



ISPOR - Republic of Macedonia
Regional Chapter



Abstract Book



24 - 27 April

Ohrid, R. Macedonia

Hotel Inex Gorica



FIRST MACEDONIAN AND FOURTH ADRIATIC CONGRESS ON
PHARMACOECONOMICS AND OUTCOMES RESEARCH

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FIRST MACEDONIAN AND FOURTH ADRIATIC CONGRESS ON PHARMACOECONOMICS AND OUTCOMES RESEARCH

Dear Sir/Madam,

It gives us great pleasure to inform you that the First Macedonian and Fourth Adriatic Congress on Pharmacoeconomics and Outcomes Research will be held in Ohrid, Republic of Macedonia, from 24-27 April, 2014. Organisers of the Congress are ISPOR, Republic of Macedonia Chapter and Section for Pharmacoeconomics and Outcomes Research of the Croatian Society for Clinical Pharmacology and Therapeutics. ISPOR Chapter, Bosnia and Herzegovina and ISPOR Chapter, Serbia, play the role of supporting organisers. The main topics of this Congress on Pharmacoeconomics and Outcomes Research will enrich and fortify regional cooperation. The promotion and cooperation of the ISPOR CEE network at this Congress are also of particular importance and interest. Different topics will be covered through lectures, poster presentation and workshops. The programme will include health economy and health policies, Pharmaceutical Parallel Trade, Cost-Effective Use of Medicines, Generic and Biosimilar Drug Policies, HTA and low income countries, Health Economy and Personalized Medicines and others. The opening day of the Congress will be marked by a specific educational course on pharmacoeconomic methods and studies. Sharing different experiences is one of the most significant aspects of the Congress, thus we invite you to take an active part at this assembly. It will be our pleasure to share the latest discoveries and experiences in the field of Pharmacoeconomics and Outcome Research. We are looking forward to spend quality time working and socialising with you.

Prof. Ljubica Suturkova, PhD

President,
ISPOR –Republic of Macedonia
Regional chapter

Prof. Dinko Vitezic, MD, PhD

President, Section for
Pharmacoeconomics and Outcomes
Research, Croatian Society for Clinical
Pharmacology and Therapeutics,
Croatian Medical Association

PROGRAM

Thursday 24.04.2014

09.00 - 18.30 Registration

14.00 - 18.00 Pre-congress course :

Zoltan Kalo (Hungary) & Dinko Vitezic (Croatia)

How pharmacoconomics should be applied to support
decisions in lower income European countries ?

18.30 - 19.15 Opening ceremony

19.15 - 20.00 Plenary lecture

Chairpersons : Dinko Vitezic & Ljubica Suturkova

Zoltan Kalo (Hungary)

Benefits of investment into modern medicines in
Central-Eastern European countries

20.30 Welcome cocktail

Friday 25.04.2014

08.00 - 18.30 Registration

08.30 - 09.15 Plenary lecture

Chairpersons: Igor Francetic & Vladimir Zah

Finn Kristensen (Denmark)

Current trends and future prospects of
Pharmacoeconomics and outcomes research – with
special reference to health technology assessment.

09.30 - 11.30 Session 1

Health economics aspect of personalized medicines

Chairpersons : Aleksandar Dimovski & Aleksandar Knezevic

Dinko Vitezic (Croatia)

Factors influencing pharmacoeconomic assessment
of new drugs in diabetes mellitus treatment

Czech Maricin (Poland)

Health economic aspects of personalized therapy in diabetic patients

Hren Rok (Slovenia)

The importance of pharmacoeconomic modeling in
assessing costs of asthma treatment

Zlate Stojanovski (Macedonia)

Prophylactic use of ciprofloxacin in stem cell recipients
reduce associated cost of stem cells transplantation

Jasminka Krehic (Bosnia and Herzegovina)

Ethical Considerations of Personalized Medicine

11.30 - 12.00 Coffee break (Sponsored by Alkaloid)

12.00 - 13.30 Session 2

HTA implementation in lower income European countries

Chairpersons : Rubin Zareski & Carmen Kostrencic

Tomek Dominik (Slovakia)

Application of Pharmacoeconomics and HTA in Drug
and Health Policies in Slovakia

Atanasievic Dragana (Serbia)

HTA implementation in Serbia

Tarik Catic (Bosnia and Herzegovina)

HTA in Bosnia and Herzegovina

Merjem Hadzi Hamza (Macedonia)

Ethical principles promoting Good Governance in the
Public Pharmaceutical sector and their impact on
Health economics

13.30 - 14.15 Alkaloid satellite meeting

14.15 - 15.15 Lunch

15.15 - 16.15 Poster session

16.30 - 19.30 Novo Nordisk satellite meeting

**Health economic properties of novel,
ultra-long lasting insulin**

17.30 - 19.30 Session 3

Improvement of generic and biosimilar drug policies

Chairpersons : Ljubica Suturkova & Dinko Vitezic

Goznalo Calvo (Spain)

Biosimilar medicinal products : from their

Drug-regulation to their market-place

Borut Strukelj (Slovenia)

Biologics and biosimilars – why the principles of
generics do not apply?

Vladimir Zah (Serbia)

Pricing and Reimbursement related to generic and
biosimilar products in CEE region

Viktorija Erdeljic Turk (Croatia)

Generic and therapeutic drug substitution

Aleksandra Grozdranova (Macedonia)

Biosimilars in Republic of Macedonia – licensing and
market access

Saturday 26.04.2014

08.00 – 18.30 Registration

08.30 – 10.30 Session 4

Role of health insurance of the cost – effective use of medicines

Chairpersons: Guenka Petrova & Robert Likic

Maarten Postma (Netherlands)

Pharmacoeconomic evaluation in process of introducing new vaccines in National
Program of immunization

Stephan Bevan (UK)

Work Disability Related to Musculoskeletal Disorders:

Assesing the burden and identifying solutions in Slovenia and the wider EU

Maja Parnargieva – Zmejkova (Macedonia)

The role of the HIFM on the effectiveness and rational use of medicines in Republic of Macedonia

SLobodanka Bolanca (Croatia)

Value of innovation in pharmaceutical sector in Croatia

Rubin Zareski (Macedonia)

Pharmaceutical pricing – a continuing crisis

10.30 -11.00 Coffee break (Sponsored by Pliva – Teva)

11.00 – 13.15 Session 5

Economic impact of pharmaceutical parallel trade/External reference pricing

Chairperson: Zoran Sterjev & Slobodanka Bolanca

John Yfantopoulos (Greece)

Economic impact of pharmaceutical parallel trade

Livio Garattini (Italy)

Risk – sharing agreements in Italy

Slobodanka Bolanca (Croatia)

TBC: Ensuring Patient Supply of Innovative Pharmaceutical Products in EU – is there any room for improvement?

Juril Furst (Slovenia)

The introduction of therapeutic reference pricing system in Slovenia

Guenka Petrova (Bulgaria)

The current pricing and reimbursement system for pharmaceuticals in Bulgaria

Vesna Nasteska (Macedonia)

Pharmaceutical Parallel Import in the Republic of Macedonia

Biljana Dimitrova (Macedonia)

Methodology for the manner of creating prices of medicines in Republic of
Macedonia

13.15 – 14.15 FarmaBrend Nova – satellite meeting

**Including new, innovative drugs on reimbursements list of NHIF – a need of
financial burden**

14.15 – 17.00 Lunch/Sightseeing Ohrid

17.15 – 19.15 Session 6

Applied pharmacoeconomics

Chairpersons: Stevce Acevski & Viktorija Erdeljic

Aleksandar Knezevic (Croatia)

Comparison of efficacy and cost of antihypertensive therapy with fixed – dose
combination versus free drug combination

Robert Likic (Croatia)

Cost effectiveness of fosfomycin use for uncomplicated urinary tract infections
cause by microbial strains producing extended spectrum beta – lactamases

Sonja Genadieva Stavrik (Macedonia)

New treatment approaches in multiple myeloma patients – new drug, new price
and new quality of life. What do we gain?

Vjollca Qerimi (Macedonia)

Evaluation of decision – analytic models for the treatment of multiple myeloma

Harasani Hudhra Kleida (Albania)

Potentially inappropriate prescribing identified by two different tools and health
outcomes assessment

Hana Kalinic Grgorinic (Croatia)

Pharmacoeconomics of the short – term prophylaxis of the HAE attacks

Igor Kikerkov (Macedonia)

Outsourcing in pharmaceutical industry

20.00 – 23.20 Congress dinner

Sunday 27.04.2014

09.00 – 10.30 Session 7

ISPOR CEE Network – regional collaboration to facilitate evidence based policy

Vladimir Zah (Serbia)

Overview of ISPOR CEE Network

Ljubica Shuturkova

Importance of ISPOR CEE Network for Macedonia

Guenka Petrova (Bulgaria)

ISPOR CEE Network current situation for Bulgaria

Zoran Sterjev (Macedonia)

ISPOR CEE research committee participation from R.Macedonia

Tarik Catic (Bosnia and Herzegovina)

ISPOR CEE educational activity and research projects in BiH

11.00 – 11.30 Closing Ceremony

ABSTRACTS¹

¹ The abstracts are presented as received by the corresponding authors. The Scientific Board of the Congress does not take any responsibility for the content of the presented papers.

O.P.1

**HOW PHARMACOECONOMICS SHOULD BE APPLIED TO SUPPORT DECISIONS
IN LOWER INCOME EUROPEAN COUNTRIES?**

Zoltán Kaló¹, Dinko Vitezic²

¹Professor of Health Economics (EötvösLoránd University; Syreon Research Institute)

*²Professor of Clinical Pharmacology (University of Rijeka, School of Medicine and Rijeka
University Hospital Center)*

As health care resources are limited all over the world, reimbursement and formulary listing of new medicines is subject to their cost-effectiveness and affordability in more and more countries. The need for pharmacoeconomic evidence fundamentally changes the algorithm of coverage decisions, therefore medical professionals and policymakers have to be familiar with the principles of pharmacoeconomics, including advantages and limitations of different approaches to estimate the health benefit, cost-effectiveness and budget impact of medicines and the transferability of results among countries.

Synthesis of scientific evidence provides better understanding of stakeholders on the real value of innovative medical technologies. The value proposition of health technologies are illustrated by different case studies in the workshop.

In lower income European countries the major bottleneck of implementation evidence based health policy are the lack of trained health economists and local data for the adaptation of international economic models. The workshop provides practical guidance for the collection of local data in pharmacoeconomic analyses.

O.P. 2

**BENEFITS OF INVESTMENT INTO MODERN MEDICINES IN CENTRAL-
EASTERN EUROPEAN COUNTRIES**

Zoltan Kalo, Professor in Health Economics, Eötvös Loránd University, Budapest, Hungary

CEO, Syreon Research Institute, Budapest, Hungary

Due to the scarcity of healthcare resources, decision-makers often expect monetary benefits--including cost savings or productivity gain--from innovative medicines. Manufacturers try to fulfill this expectation by expressing the benefits of innovative technologies in monetary units citing approaches from the scientific literature. Unfortunately, currently available evidence has limited relevance and transferability in Central-Eastern European (CEE) countries. The presentation summarizes how innovative pharmaceuticals in CEE countries may contribute to WHO-defined health system objectives, including health gain, equity in health, financial protection, responsiveness, equity in finance and financial sustainability. References are mainly based on international examples; therefore, additional policy research from CEE countries is necessary to validate assumptions. If CEE politicians can rely on credible arguments based on local research evidence, they may improve long-term strategies and policy decisions related to healthcare innovation.

O.P.3

**CURRENT TRENDS AND FUTURE PROSPECTS OF PHARMACOECONOMICS AND
OUTCOMES RESEARCH - WITH SPECIAL REFERENCE TO HEALTH
TECHNOLOGY ASSESSMENT**

Finn Boerlum Kristensen,

EUnetHTA Secretariat, Danish Health and Medicines Authority, Copenhagen, Denmark

Keywords: Health technology assessment, pharmacoeconomics, clinical epidemiology, health policy

The life-cycle approach to the assessment of technologies and the emphasis on real world data to substantiate the effectiveness and cost-effectiveness of technologies has a high influence on current development trends. This presentation will navigate between several coordinates such as 1) trends in health policy and clinical management, 2) trends in regulatory assessment for marketing approval and beyond, 3) trends in HTA at scientific and policy levels, 4) trends in epidemiology and clinical epidemiology in the light of e-health and health informatics.

O.P.4

**FACTORS INFLUENCING PHARMACOECONOMIC ASSESSMENT OF NEW
DRUGS IN DIABETES MELLITUS TREATMENT**

Dinko Vitezić

University of Rijeka Medical School and University Hospital Centre Rijeka, Rijeka, Croatia

According to the latest WHO estimate diabetes mellitus (DM) epidemics data showed that the number of patients would increase to at least 300 million by 2025 (30 million in 1985; 135 million in 1995). The global health expenditure on DM is calculated to total at least 376 billion USD in 2010 and 490 billion USD in 2030, i.e. 12% of the health expenditures and 1330 USD per person. The largest components of medical expenditures are hospital inpatient care, prescription medications to treat the complications of diabetes, antidiabetic agents and diabetes supplies, physician office visits, and nursing/residential facility stays.

Because of limited health care funding, health care decision makers are increasingly concerned to understand the clinical and economic impact of interventions used to manage DM. Pharmacoeconomic evaluation in relation to new antidiabetic medications includes the long-term benefits of reduced micro- and macrovascular complications, costs of side-effects and changes in drug utilisation patterns, in addition to the immediate drug budget impact. To help decision makers optimizing the allocation of healthcare resources health economic modelling are employed.

Cost-effectiveness is expressed as an incremental cost-effectiveness ratio (ICER), the ratio of change in costs to the change in effect. Quality of life is reduced by DM-related long-term macrovascular complications such as coronary heart disease including angina pectoris, myocardial infarction, congestive heart failure, and micro-vascular complications such as nephropathy, retinopathy and nephropathy. Long-term clinical studies like UKPDS (T2 DM) and DCCT (T1 DM) demonstrated that good glycaemic control, measured by HbA1c (surrogate marker) level reduction, reduces the risk of DM complications. Thus, the impact on HbA1c reduction is widely accepted as efficacy marker in clinical and cost-effectiveness assessment of new antidiabetic agents.

Efficacy of DM medications should always be assessed against the risk of hypoglycaemia. Even more, incidence of hypoglycaemia shall be used in evaluation of direct treatment costs because severe hypoglycaemia imposes a major economic burden on healthcare systems, with the highest proportion of direct costs resulting from the small number of patients who are admitted to hospital. Furthermore, because subsequent follow-up also incurs costs, hypoglycaemic episodes requiring professional attendance outside hospital generate greater costs than those treated in the community by relatives or friends. Although people with T2 DM

are often perceived to be at low risk of developing severe hypoglycaemia, studies have shown that increasing duration of insulin treatment is the important factor that determines the risk of experiencing severe hypoglycaemia.

In addition to long-term complications and hypoglycaemic episodes, impact of weight reduction is also being considered recently in cost-effectiveness assessments of newer antidiabetic agents.

Optimal glycaemic control accompanied with low frequency of hypoglycaemia is the key to prevent long-term diabetes complications, which are major drivers of diabetes related costs. Thus, cost-effectiveness of new drugs in diabetes mellitus treatment should be assessed against these two parameters.

O.P. 5

Czech Maricin (Poland) – Health economic aspects of personalized therapy in diabetic patients

O.P.6

**THE IMPORTANCE OF PHARMACOECONOMIC MODELING IN ASSESSING
COSTS OF ASTHMA TREATMENT**

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Background/aims: In this paper, we critically evaluated the costs of asthma treatment when using currently available fixed-dose combinations of long-acting beta agonists (LABAs) and inhaled corticosteroids (ICSs) in Slovenia.

Methods: In order to take into account the complexity of asthma treatment and particularly accompanying dose titration, we applied a Markov model to the cohort of 12,300 patients based on the results of seminal study GOAL (Gaining Optimal Asthma Control). The comparative analysis included the following fixed-dose combinations of ICS/LABA: fluticasone propionate/salmeterol (FP/S), budesonide/formoterol (BUD/F) and beclometasone dipropionate/formoterol (BD/F). In the analysis, we assumed that the clinical efficacy and incidence of adverse events of fixed-dose ICS/LABA combinations were identical. The time horizon was set at 3 years.

Results: Model analysis showed that the three-year costs of FP/S were lower than the three-year costs of BUD/F and BD/F by 31% (€666 per patient) and 22% (€405 per patient), respectively. The costs of treatment with FP/S were lower than with BUD/F and BD/F for patients who were previously treated both with low/medium doses of ICSs (≤ 500 mg equivalent dose of BD) and high-doses of ICSs (> 500 mg and ≤ 1000 mg equivalent dose of BD). The treatment costs of FP/S were also consistently lowest irrespective of whether patients remained on the therapy for one, two or three years.

Conclusions: Pharmacoeconomic models are widely used when introducing new health-care technologies to the market, however, the same methodology should be applied when the goal is to objectively and systematically assess the costs of existing drugs.

O.P.7

**PROPHYLACTIC USE OF CIPROFLOXACINE IN STEM CELL RECIPIENTS
REDUCE ASSOCIATED COST OF STEM CELLS TRANSPLANTATION**

Zlate Stojanoski, Sonja Genadieva-Stavrik, Aleksandra Pivkova, Lazar Cadievski, Borce Georgievski

University clinic of Hematology, University St's Cyril and Methodius, Skopje, R.Macedonia

Key words: ciprofloxacin, infections, stem cell transplantation

Introduction: Hematopoietic stem cells transplantation (HSCT) is an important treatment modality and expensive lifesaving procedure for many benign and malignant hematologic and non-hematologic diseases. During a last 5 decades there has been a dramatic increase in the number of stem cells transplant procedures performed worldwide. However, an increasing use of transplantation has economic consequences. According to an Agency for Health Care Research and Quality report, HSCT generated the most rapid increase in total hospital costs from 2004 to 2007 with a growth rate of 84.9% and \$1.3 billion spent in 2007 in the USA. It was estimated that 25.6% of this increase was the result of an increase in mean cost of hospital stays, and 59.3% was the result of an increase in the number of hospital days. According to study performed in Sweden in 2009, the total costs included selection and harvesting of stem cells, transplantation and 1-year follow-up the average costs per patient were 45,670 € for auto-SCT and 101,919 € for sibling allo-SCT. The costs of transplantations from unrelated donors were much higher: 171,478 € for allo-SCT-MUD and 254,689 € for allo-SCT-UCB. Hospital inpatient days together with laboratory and other activities were the main cost drivers across all types of SCT. Common post-transplantation complications, such as infections and GVHD, have been shown to be significant cost drivers. Bacterial infections remain one of the main causes of further morbidity and mortality in patients treated with HSCT. Different strategies, such as barrier nursing, sterile room conditioned with HEPA filtration, hematopoietic growth factors, intravenous immunoglobulins, and antimicrobial agents, have been proposed in order to decrease infections in this patients. Lee et al found infection, veno-occlusive disease, acute GVHD, and death added between \$15 300 and \$28 100 each to allogeneic transplantation costs in USA. Similar findings were reported by Esperou et al who reported an addition of 20 000 Euros because of occurrence of GVHD and infections in Europe.

Results and discussion: Aim: to present the use of fluoroquinolones (Ciprofloxacin 1000mg/day) as antibacterial prophylaxis in stem cell recipients and the influence on the frequency of the febrile episodes, serious Gram-negative bacterial infections, and hospital stays after stem

cell transplantation. Results: during a 13 years period, from September 2000 until September 2013 we have performed 267 stem cells transplant procedures in 253 patients with different hematological malignancies in our center. Autologous: 194 Allogeneic:73. Peripheral blood stem cells: 239 and Bone marrow: 28 transplantations. The patients were treated in sterile room conditioned with HEPA filtration. They received different chemotherapeutic regimen as conditioning therapy prior transplantation according to underlying disease. As an antibacterial prophylaxis we use Ciprofloxacin 1000mg./day. until neutrophil recovery. Median day of engraftment was: day +11 in both groups. Febrile episodes were presented in 35% of autologous and in 64% of allogeneic recipients, with onset on day +5 and median duration 4 days. Gram-negative bacteria were isolated in 27% of all isolates, Gram-negative bacteraemia: 14,8% of them. Serious infections due to Gram-negative bacteria: sepsis in 2 patients and pneumonia in 4 patients. Fatal outcomes: 2 patients (*Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* sepsis). Median hospital stays were median 14 days in autologous recipients, while 18 days in allogeneic recipients.

Conclusion: Anti-infective prophylaxis with Ciprofloxacin was shown to be effective in reducing febrile episodes, bacterial infections, especially bloodstream infections caused by Gram-negative bacteria and the use of empirical first-line antibiotic therapy. Our results confirm that prevention and better management of infective complications can improve clinical outcomes as well as reduce the associated costs of stem cells transplantation.

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O.P.8

DECISION-ANALYTIC MODELING STUDIES FOR THE TREATMENT OF
MULTIPLE MYELOMA: AN OVERVIEW

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Key words: decision-analytic modeling, multiple myeloma, treatment, systematic literature search

Introduction: Multiple myeloma (MM) is a hematological malignant plasma cell neoplasm presenting with a clonal proliferation of plasma cells producing monoclonal immunoglobulin. In recent years, the therapeutic management of MM has changed, when several new drugs were introduced into the clinical routine and resulted in convincing improvements in patient outcomes, and in new treatment combinations with different benefits, harms and costs. We provide an overview on published decision-analytic models evaluating treatment strategies for MM focusing on the structural and methodological modeling approaches and to derive recommendations for future MM models evaluating different treatment regimens. We performed a systematic literature search in the electronic databases PubMed/Medline, NHS EED and the Tufts CEA Registry to identify published studies evaluating MM treatment strategies that used mathematical decision-analytic models. To meet the inclusion criteria, the studies had to evaluate different treatment strategies and report relevant clinical health outcomes. We used standardized forms for data extraction, description of study design, methodological framework, and data sources.

Results and discussion: We identified eleven different decision-analytic modeling studies. All studies included an economic evaluation. The modeling approaches varied considerably (decision tree, cohort state-transition (Markov) model, discrete event simulations, partitioned survival analyses and area under the curve models). Analytic time horizons ranged from seven years to lifetime. Ten studies adopted a third-party payer perspective (e.g., governmental payer, health-care system); only one model was conducted from the societal perspective. Health outcomes included (overall, median, progression-free) survival, number needed to treat, time to discontinuation of treatment, life expectancy, and quality adjusted life-years. Compared treatment strategies included lenalidomide, dexamethasone, bortezomib, melphalan, prednisone, thalidomide, haemodialysis, bone marrow transplantation, zoledronic acid, and clodronate. Model validation was only mentioned in the discussion when comparing the results with other cost-effectiveness studies.

Conclusion: We identified several well-designed models for MM treatment strategies evaluating relevant health outcomes and reporting results for cost-effectiveness/cost-utility analyses. Most of the studies were not comparable due to different treatment strategies, target population, transferability and settings. The quality and details of reporting varied considerably and in some cases the models were not sufficiently described. Regarding future models, our findings support the recommendation for an explicit model description including all relevant parameters according to the ISPOR-SMDM Modeling Good Research Practices Task Force guidelines.

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O.P.9

**LIMITS OF APPLICATION OF PHARMACOECONOMICS AND HEALTH
TECHNOLOGY ASSESSMENT IN DRUG AND HEALTH POLICIES**

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The example of Slovakia shows that the drug policy is shifted more and more towards objective measures with the help of pharmacoeconomics or HTA, actually without scientific evaluation of the results. The P&R policy in Slovakia has gone through several changes during last five years. The new legislation is dramatically influencing the P&R approval of new, particularly high priced medicines and new indications. This will challenge payers, health care providers, industry and patients to find new ways to maintain the availability of innovative treatment. Out of 12 new EU member states (accessed in May 2004 or later) HTA was applied in 10 of them; in 8 as a light version and in 2 as a robust NICE-like version. HTA has an impactful position in 6 of them (Estonia, Hungary, Latvia, Poland, Slovakia and Slovenia). Threshold is officially published in primary legislation in 2 countries (Poland, Slovakia). There are three main pillars on provision of healthcare - access, quality and costs. Overall, as well as in Slovakia, this is challenged with focus on transparency, predictability, affordability and resource allocation. We are facing ongoing discussions on free market principles in healthcare, profit generation, redistribution, institutional and individual capabilities. The drug policy is acknowledged as one of the elements of effective and efficient resources allocation. In Slovakia the pharmacoeconomics principles have been introduced as mandatory for the pricing & reimbursement process since 2006, however, the full impact was reached only recently, with an implementation of ICER and/or cost-per-QALY thresholds into formal legislative framework. However, we must acknowledge that ICER is insufficient as a measure for objective evaluation of the value of innovation. There are fundamental differences in the potential value of threshold for the cost per QALY due to significant differences in utility perceptions (e.g. mild hypertension patient vs. final stage metastatic malignant melanoma patient), different healthcare provision settings (ambulatory vs. hospital, acute vs. long-term) and between different healthcare systems. However, the society priorities are changing. Societal values such as equity, preference for life-saving treatments, rare diseases issues are demanded more often. Patient-centered approach is to be incorporated into the assessment of innovations. Those requirements are pre conditions of well-performed health technology assessment, and any further appraisal of health technologies should have a base in HTA implementation.

O.P.10

Atanasijevic Dragana (Serbia) – HTA implementation in Serbia

O.P.12

Tarik Catic (Bosnia and Hercegovina) - HTA in Bosna and Hercegovina

O.P. 13

**BIOSIMILAR MEDICINAL PRODUCTS: FROM THEIR DRUG-REGULATION TO
THEIR MARKET-PLACE**

Gonzalo Calvo

The establishment of a clear regulatory framework for biosimilars has indeed been a key step to promote the development of these drugs. It has been estimated that the European biopharmaceuticals market accounts for approximately 45 per cent of the global market and pharmaceutical expenditure in general is constantly increasing in Europe. For many years the increased availability of generic medicines has had a major contribution to control the overall health costs in medicinal products and, therefore, it could be considered that biosimilars would have the same positive effect. However, the market for generics in Europe is quite split and their introduction and impact is highly variable among the different countries. For instance, Germany and the United Kingdom have a well-developed generics market and prices for medicines are high in general while in Spain, Italy and France generics did not account for a significant proportion of the pharmaceutical market until recently. Differences in pricing systems, incentives, promotion and even cultural aspects may result in this fragmented picture. It is possible that the use of biosimilars followed the same pattern as generic medicines. Additionally, the marketing and launch of biosimilars needs a different strategy than generics (as marketing, use, patient support and post-marketing activities such as pharmacovigilance need more resources and experience). However it is too early to say and we probably need a few more years to identify the real place of biosimilars in particular therapeutic areas.

O.P.14

**BIOLOGICS AND BIOSIMILARS - WHY THE PRINCIPLES OF GENERICS DO
NOT APPLY?**

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Key words: medicinal, biologicals, biosimilars, generics, safety, comparability

Introduction: In a field of biological medicines, last five years were dedicated to similar biological medicinal products, commonly referred to as biosimilars. They represent a copy version of an approved original biologic medicine whose data protection has expired. However, biosimilars cannot be assumed as completely identical to the reference product, nor can two different biosimilars be considered equivalent. In principle, biosimilars are the biologic drugs that might be regarded as biogenerics.

Discussion: From biotechnological and clinical points of view, biologicals are derived from living cells or organisms and are composed of highly complex molecular entities (proteins, glycoproteins, lipoproteins), that may be difficult to be fully characterized. Due to the substantial variability of biologic expression system as well as manufacturing process, almost all complex biosimilars and biologicals display a certain degree of microheterogeneity, not only between each biosimilar and its reference product but also between different batches of the same product. According to the general definition of the generic medicines that should possess identical molecular structure it has been through years clearly demonstrated that general definition of generics cannot be simply transferred into the field of biologics. Consequently, only physicochemical identification and demonstration of similar bioequivalence profile of biosimilar is not sufficient to conclude on therapeutic equivalence. Therefore, biosimilars need to be developed and characterized on a more extensive head-to-head comparison with the reference product, included clinical investigations in order to demonstrate the comparability in terms of quality, efficacy and safety. Since 2007, biosimilars have been approved for use in patients in the European Union (EU). European experience provides several base points as the United States (US) healthcare system prepares for biosimilar approvals. These lessons emphasize the need for adequate efficacy and safety studies, post-marketing surveys and a robust pharmacovigilance system that can accurately track and trace biologics, including biosimilars and their reference products, from the patient to the manufacturer. The marketing authorization holder's application for the biosimilar approval must contain biosimilarity information based on data derived from analytical, animal, and clinical studies. Clinical studies

should include an assessment of immunogenicity, pharmacokinetics, pharmacodynamics, and address one or more indications licensed for the reference product.

Conclusions: Based on the data presented, we demonstrate that the general principle of generic small chemical entities cannot apply to biosimilars. In the presented article, we will elaborate the basic requirements for biologicals and biosimilars in terms of structure-activity relationships, safety and potentially developed immunological response that might influence on the overall quality of the product.

O.P.15

**PRICING AND REIMBURSEMENT RELATED TO GENERIC AND BIOSIMILAR
PRODUCTS IN CEE REGION**

Vladimir Zah

Due to the differences in biological and chemical agents, biosimilars require a special approach for the registration of biosimilar and organization of post-marketing studies. Question is at which product phase (3 or 4) can biosimilar with certainty be released as a substitute to expired innovative drug?

Author will further discuss the political and economic pressures to increase access to healthcare, the gradual implementation of reduced requirements for less complex biosimilars in Latin America.

Impact of International Reference Pricing in CEE region is to be further examined.

Potential end and it's impact of CEE Protectionist market policies that are implemented will be discussed.

Audience participation is anticipated.

O.P. 16

GENERIC AND THERAPEUTIC DRUG SUBSTITUTION

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Key words: generic drug substitution; therapeutic drug substitution; Croatia, clinical appropriateness; cost-minimization

Introduction: There is considerable debate concerning the place of generic (from a brand to generic product) and therapeutic substitution (switching to a cheaper product usually within the drug class, eg. statins, proton pump inhibitors, drugs that affect the rennin-angiotensin system). Generic substitution is promoted by the Croatian Health Insurance Fund in Croatia in the primary health care setting, and recently in the secondary healthcare setting by establishment of centralized drug procurement system. It is estimated that generics constitute 50% of overall drug consumption in Croatia. Therapeutic substitution is more contentious as direct evidence to support equivalence is lacking. However, the price differentials makes it an attractive application of cost-minimization analysis for the more efficient use of health resources.

Results and discussion: Here we explore the existing open questions taking into consideration the clinical appropriateness and safety of generic and therapeutic switching, from an individual patient perspective and health service perspective. Although substitution may affect individual patients, it might be a price worth paying given the opportunity cost associated with the use of medicines that are clinically no better than cheaper alternatives. However, tensions are created by the promotion of the concept of patients choice at the same time. We review clinical areas or drug types where brand prescribing may be considered preferable because of the possibility of therapeutic inequivalence or potential for confusion (eg. medicines with a narrow therapeutic window where there is evidence regarding the risk of adverse patient reaction or inadequate efficacy, vaccines, biosimilars).

Conclusion: Generic substitution is almost universally accepted as desirable and cost reducing. Therapeutic substitution, although not as widely accepted, allows also considerable cost savings to be made. The trade-of is patient choice vs. rational fund spending. Arguably, for any publicly funded healthcare system, the latter has to be the priority.

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O.P.17

**BIOSIMILARS IN REPUBLIC OF MACEDONIA – LICENSING AND MARKET
ACCESS**

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Biosimilars presents significant clinical, regulatory and economical issue which is still discussed in Europe. Due to their complex structure and the processes of production, biosimilars are not identical copies of biological medicines and therefore the generic approach cannot be applied. The patents of a number of biologic medicines have already expired or are due to expire, which has led to an increased interest in the development of biosimilars. The licensing of biosimilars is based on abbreviated registration process and biosimilar manufacturers must submit robust data to demonstrate a product's efficacy and safety profile and provide substantial data to show that its product is sufficiently similar to the original product. Since biosimilars are a relatively new and emerging market, regulatory guidelines and standards are still being developed. Within the European Union, Member States are generally responsible for implementing regulation adopted at EU level including development, authorization and manufacturing of biosimilars. The first biosimilar guidelines was created in EMA in 2005, followed by the first approved biosimilar products in 2006 and at the end of 2013 the number of biosimilar products approved by the EMA was seventeen. Regulation has evolved rapidly with many countries establishing national guidelines based on the WHO and EMA framework. Although many things including regulations for licensing of biosimilars are harmonized within the EU, the attitude towards biosimilars and their substitution in different countries of the EU varies widely. The regulatory aspects of licensing of biosimilars in countries like Macedonia where the presence of biosimilars is still limited, are in development, but there is lack of official guidelines for substitution or interchangeability between biosimilars and biological reference products.

O.P. 18

**ETHICAL PRACTICES PROMOTING GOOD GOVERNANCE IN THE PUBLIC
PHARMACEUTICAL SECTOR AND THEIR INFLUENCE IN HEALTH
ECONOMICS**

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Key words: **pharmaceutical procedures, drug chain, economic impact, unethical practices,**

Ethical practices promoting Good Governance are an important factor affecting economic growth and sustainable development at every level and within all sectors of society. Pharmaceutical sector is one of the key elements of the health system with a great influence on public health. As acknowledge, the pharmaceutical sector is very complex and highly regulated in most economies. The complex nature of the pharmaceutical sector comprises broad spectrum of functions. Thus, the 'drug lifecycle' includes many different steps beginning with the research and development of new drugs through their manufacturing, clinical trials, marketing authorization, procurement, selection, distribution, inspection, promotion, pricing, reimbursement and ending with rational drug use and pharmacovigilance. In principle, each step in the drug chain involves variety of procedures, applied standards, policy instruments, competent regulatory authority and professional expertise. Considering the value of the global pharmaceutical market it is estimated to reach over 600 billion US dollars while health expenditures each year exceed the figure of 3 trillion US dollars. However, it is disappointing to note that imposing tangible assets related to the pharmaceutical market have often been targeted for abuse and from this perspective the pharmaceutical sector is becoming highly vulnerable to unethical practices. These unethical practices may have significant economic and health impact by causing irreversible lost of health funds and affecting the quality of public health, as well. This has become an important issue since in most developing countries pharmaceutical expenditure and drug procurement account for 20-50% of total public health budget. Improper management of public funds reduces the government capacity to provide good - quality essential drugs and leads to irrational use of drugs too. Therefore it is of crucial importance to meet ethical criterions during implementation of different procedures related to pharmaceutical sector. In addition, each specialized professional activity in this domain requires a combination of knowledge, expertise, skills, experience and the availability of timely, non-discriminatory, transparent and predictable processes.

The reasons worldwide considered responsible for the appearance of unethical practices are: (1) Imprecisely defined and documented procedures (2) Lack of control mechanisms (3) Lack of transparent procedures. Imprecisely defined and poorly documented procedures, lack of control mechanisms as well as lack of transparency always causes a delay and bureaucratization of procedure implementation and play an significant role in shaping economic lost. This can further increase the vulnerability to unethical practices. Therefore it is particularly important equal sharing of information's between all participants in the drug chain so they can make decisions based on relevant information and evidence.

Many models are globally recommended in order to prevent unethical practices worldwide in pharmaceutical sector.

(UNESCAP)-Figure 1.

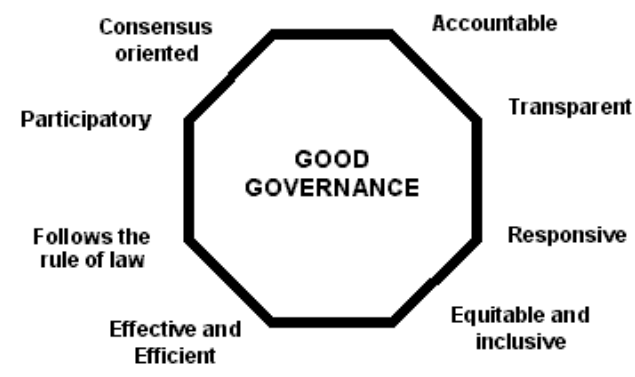


Figure 1: Elements of Good governance

From the perspective of good governance, at first it is fundamental need to have policy framework, stringent regulations, and procedures that improve the governance of drugs chain and promote access to drugs with proven high quality. In order to improve the good governance in pharmaceutical sector Ministry of Health of Republic of Macedonia with WHO support has published the, Ethical framework for Good Governance in public pharmaceutical sector". „Good governance” refers to the implementation of appropriate policies and procedures that ensure the effective and ethical management of pharmaceutical systems and drug supply systems in a manner that is transparent, accountable, follows the rule of law and minimize unethical practices. The World Health Organization (WHO) has developed a technical package which helps Countries to establish Good Governance for Medicines (GGM) program at national level. The establishment of GGM program is an essential tool which can be

helpful to all health systems to improve all functions within the health sector and have positive impact on health economics.

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**PHARMACOECONOMIC EVALUATION IN PROCESS OF INTRODUCING NEW
VACCINES IN NATIONAL PROGRAM OF IMMUNIZATION**

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Health economics is becoming increasingly important in the evaluation of vaccination strategies, for example, in the context of formal health-technology assessments of new vaccines. Notably, guidelines for health economics are omnipresent and often developed for therapeutic pharmaceuticals (pharmacoeconomics). It is debated in how far these guidelines can straightforwardly be applied to vaccines as well. It is well known they generally impact quite differently on vaccines than they do concerning therapeutics pharmaceuticals. Issues of such debate concern discounting, the perspective chosen, the desired time horizon and type of clinical endpoints warranted. The debate will be illustrated using examples from newly available vaccines, such as the rota and HPV-vaccines, but also apply to already longer existing vaccination programs for various respiratory infections. The aim is to identify the issues of relevance and suggest ways for better precision in the guidelines to optimally accommodate economic evaluations of vaccines as well, as in the current situation these guidelines seem to fail in that respect.

O.P. 20

**WORK DISABILITY RELATED TO MUSCULOSKELETAL DISORDERS:
ASSESSING THE BURDEN AND IDENTIFYING SOLUTIONS IN SLOVENIA AND
THE WIDER EU**

Stephen Bevan

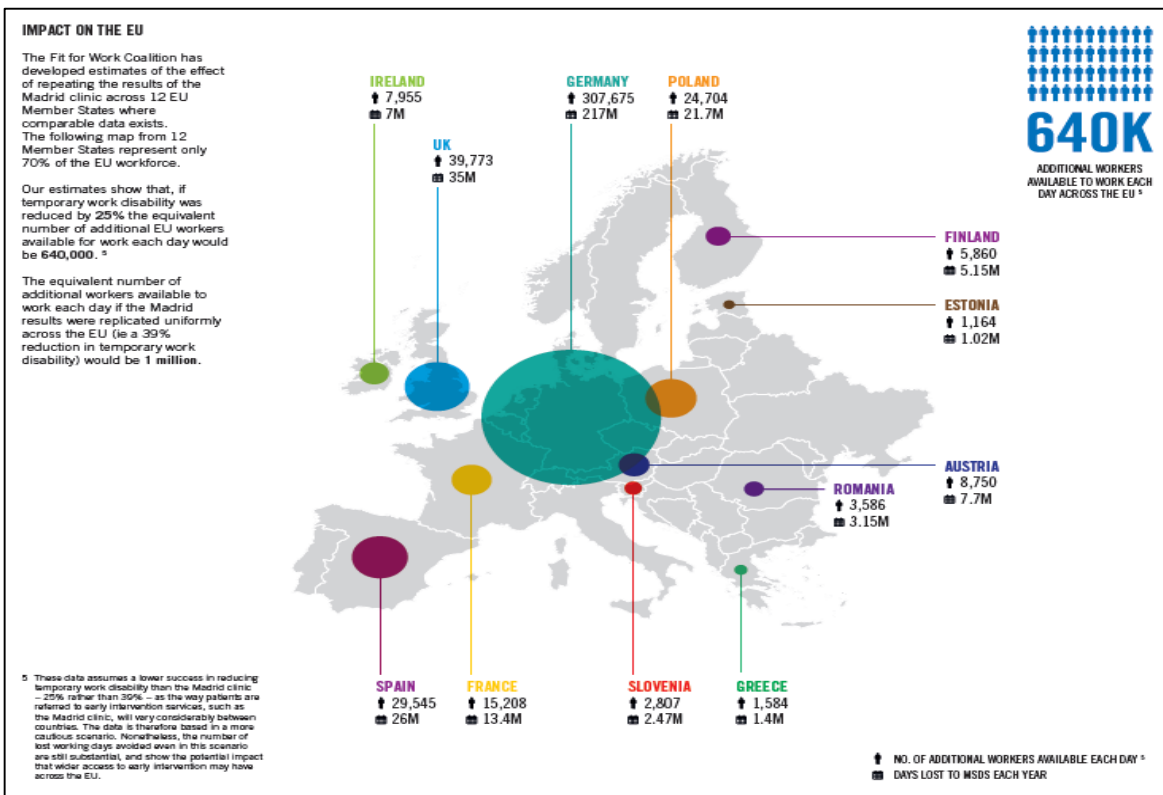
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Keywords: Musculoskeletal; Work Ability; Slovenia; Productivity; Early Intervention

Introduction: The global burden of disease data show that musculoskeletal disorders (MSDs) are the largest contributors to the burden of years lived with disability (YLDs). The impact on lost productivity in the EU is also substantial as MSDs affect over 40m workers (at an annual cost of €240 bn) and cause 49% of all lost working days. As the EU workforce ages and as the burden of chronic illness grows it will become an economic necessity to devise and implement cost-effective and timely interventions to reduce work disability and sustain productivity levels. This paper will examine the prevalence and impact of MSDs in the EU and, using research conducted into the Slovenian labour market as a case study, will highlight how healthcare decision-making, clinical practice and welfare policy might better coordinate to improve outcomes for people living with MSDs.

Results: A multi-method study has been conducted into the burden of MSDs in the Slovenian workforce as part of a pan-European study called 'Fit for Work Europe'. In Slovenia, almost 50% of the workforce report having conditions such as back pain, that 2.47m working days are lost to MSDs in Slovenia each year and that MSDs overall contribute significantly to the disease burden among Slovenian citizens – affecting both labour market participation and social inclusion. The study found challenges in the measurement of MSDs in the working age population of Slovenia. It also found that improved diagnosis and early clinical interventions could significantly improve both job retention and return to work. The study calculated that a 25% reduction in temporary work disability among Slovenian workers with MSDs would allow an additional 2,800 to attend work each day.

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It also found that labour productivity among Slovenian workers with MSDs could be improved if healthcare professionals routinely considered work as a clinical outcome of care and if early clinical interventions which improved work ability were prioritised by healthcare decision-makers. Cost effectiveness data from a number of EU examples of early intervention show that returns of 9:1 are feasible.

Conclusion: The study concludes that in Slovenia – and in the wider EU – the productivity gains of early clinical interventions for people with MSDs are considerable and that the return on investment from such interventions should incentivise better coordinated responses from policy-makers, clinicians and employers.

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O.P. 21

**THE ROLE OF THE HIFM ON EFFECTIVENESS AND RATIONAL USE OF
MEDICINES IN REPUBLIC OF MACEDONIA**

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Health Insurance Fund of Macedonia

Key words: health insurance, HIFM, health expenditures, drug expenditures

Introduction: Macedonia has a solidarity based compulsory health insurance system, that collects the funds from health insurance contributions in form of earmarked social payroll tax, which is the main source of financing the health system. The Health Insurance Fund of Macedonia (HIFM) is a purchaser of health care services for the insured. HIFM contracts with around 3.500 health providers that provide health services and pharmaceuticals. The health insurance system covers 85% of the population, but the system enables every citizen to be insured, of actually every person living in the country is insured. Currently the HIFM Budget is 4,6% of GDP, or 22 billion MKD (357 million EUR), with pharmaceuticals accounting more than 10% (drugs used in hospitals are not included).

Pharmaceutical expenditures and consumption: Worldwide expenditure on pharmaceuticals has been increasing at a faster rate than total health spending: per capita spending on pharmaceuticals rose by more than 50% between 1995 and 2005. The system is based on a *positive list of drugs* that defines which drugs are eligible for reimbursement from the HIFM. The process of revision of the list has been reestablished and there will be 14 bodies responsible for introducing new drugs in the list.



Figure 1. Number of prescribed drugs and total expenditure for drugs

Having in mind the constant increase of the consumption and the expenditures for drugs and how serious concern is to the financial sustainability of the health system, the cost control policies are inevitable. In the Macedonian system some mechanisms for efficiency have been introduced in the past years and some are in the process of implementation in the moment.

The most important measure that significantly stopped the increase of these expenditures in 2009 and 2010 or in the beginning of the economic crises was the introduction of the *new methodology for reference pricing*. As a result of that in 2010 in comparison to the previous year the expenditures for pharmaceuticals decreased for 2,8%, while the number of prescribed drugs continued to increase.

The other mechanisms are structured in two groups

1. Measures focused on the doctors

- *Generic prescribing* has been introduced in Macedonia for several years, and as a part of that process the doctors can't suggest pharmaceutical brands and pharmacists are obliged to inform the insured about the different brand names and the difference in the price
- *Level of prescribing*. For part of the drugs on the positive list is required to be prescribed by a doctor from higher level of health care (specialist, subspecialist)
- *Guidelines for standard treatment* have been implemented by the Ministry of Health a few years ago and the role of the HIFM is to make sure there are followed by the hospitals

2. Measures focused on the consumers

- *National campaign for rational use of drugs especially antibiotics.* Macedonia is one of the countries with highest use of antibiotics. One part of the campaign is education for the final consumers but also monitoring and education for the doctors, especially the ones that over prescribe antibiotics.

Conclusion: Macedonia is a country with limited funds for health care in total, as % of GDP and also as the part of the public funds allocated to health. Despite that, in the past few years a lot has been done by the health authorities and by the Government towards containing the expenditures for pharmaceuticals without decreasing their availability. With all the measures introduced significant efficiency in the use of pharmaceuticals has been achieved. Some of the measures that are implemented in Macedonia, like the generic prescribing, even the developed countries have difficulty introducing in their systems. But there are a lot of steps that have to be completed in the future. The process of defining the medical guidelines is in halfway, but the HIFM has started the control of their enforcement in hospitals. At its beginning is a big national campaign for rational use of antibiotics accompanied with additional education focused on medical workers and the consumers that is expected to remove Macedonia from the top of the list of the biggest consumers of antibiotics. As in all health systems, the biggest challenge to come is how to finance the constant growth of health expenditures. But even within the limited resources, with a lot of work from the authorities and health institutions and cooperation with the pharmaceutical industry, positive effects for the health status of the population can be achieved.

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Slobodanka Bolanča (Croatia): Value of innovation in pharmaceutical sector in Croatia

O.P. 23

PHARMAUTICAL PRICING- A CONTINUING CRISIS

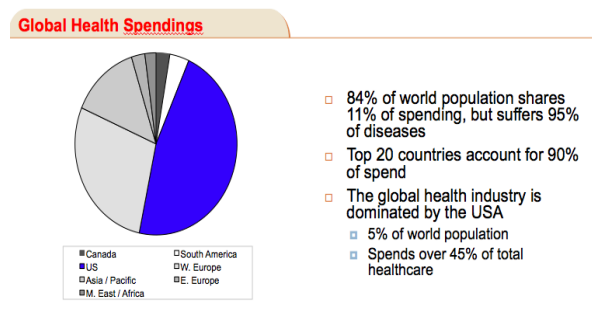
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Key words: pharmacoeconomics, drug costs, new common model, HTA

Introduction: In the last 10 years we are experiencing hidden debate where decision makers do not want to opt for the “unpopular” decisions, which need to be taken if we need a sustainable health systems. In the crisis that is being driven by external global forces that are beyond our control, spending more money will not solve the problem. Making the system sustainable requires that the Governments implement changes to the way care is funded and delivered, which limits the services provided by the state – creating new losers as well as winners. In this new environment, pharmaceutical companies will have to make major shift in the policy implementation by trading price for access to markets. Although Governments are pleased by this changed position, on the long run they will face with more problems than ever. Finding a right balance by introducing a pharmacoeconomic studies will address the problem on a long run.

New Common model: Healthcare consumes 12% of global GDP, and is a \$5.2 trillion industry. Spend is growing at average of 4% per annum, which will double expenditure in less than 20 years. By 2080, estimated 50% of world GDP will be spend on health costs (OECD analysis). Question is whether this growth is sustainable? Health players inevitably are changing the behaviour patterns, influencing the fundamental global forces that will change the way systems work. The shape of global health systems in the next 20 years will continue to undergo dramatic change. Reduction on the reliance on market forces (Obamacare), growth in importance of emerging markets, need for control of costs and increase of performance levels must lead towards new agreement of delivering the services and products and covering the costs by third party payers. It is therefore important to find a right balance between global trends, funding and expenditure. By default this requires establishment of a common Model that will implicate the Government and Pharma industry policies.



Source: WHO

The core elements of changes: Universal access to the healthcare as a human right is no longer affordable. The options are limited to the need to implement changes that will improve efficiency, control demand and finally shift the focus from the decisions that are partly rational, but also driven by societal preferences, political expediency and partisan pressure. One of potential exit solutions is to limit the scope of “Core Services” paid through taxation and to drive Government policies to focus on investments that have the biggest impact on the health of the nation. Core element for these revised policies is to focus on what really drives value in the Markets. Considering the fact that about 15% to 20% of clinical spend is wasted on efforts that are not valued by key stakeholders, urgent changes in policies are needed. To address this negative correlation, pharmacoeconomists need to focus on what really drives treatment decisions and what new data would be viewed as clinically meaningful for prescribers and value-creating for economic stakeholders. This requires:

1. continuing analysis, including assessment of the critical drivers of behavior for each stakeholder (prescriber, payor, and patient).
2. detailed comparison of competitor labels and clinical data- to further inform which efficacy and safety endpoints matter most, and maps each of the brands against their stakeholder perception mapping-
3. understanding of how competitors are perceived by each stakeholder against the most critical factors, which can help identify unmet needs, and a
4. profound understanding of real-world data on treatment decisions and outcomes.

Major challenge that we will face is the size and content of “core provision”. We need to understand that this choice is arbitrary. Eventually all health systems will converge largely onto the same system structure – the *Common Model*. As attempts of establishing of the common model expand, it will challenge the very basis of innovation funding. This will by default considerably provoke change in the policies the drugs companies strategically operate. The drugs

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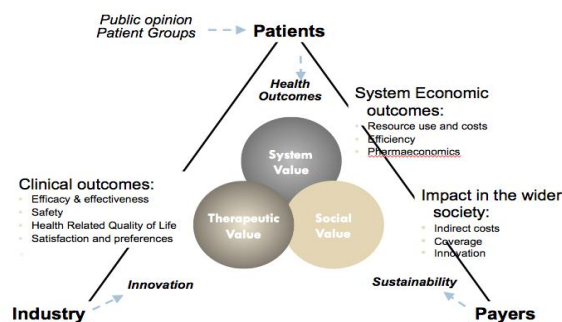
companies will no longer be able to develop and price drugs assuming model of universal reimbursement, unaffordable drugs will see price regulation, or exclusion and Companies will need to decide which segment to target. They will have to consider and weight several options:

- Low cost per unit/high volume/mass market/core service
- High cost/out of pocket funded

as consequence drug pricing will need to become far more flexible and pricing policies will be affordable against other health priorities

- Novel pricing mechanisms to meet local system needs e.g. risk based, licence based, volume based
- Pricing based on a global model to maximise overall revenue, not based on what markets can bear
- The model of innovation funding will need to be adjusted to the new reality.

Conclusion: In recent years, the pharma industry has shifted towards areas that may be excluded from core services. Partially this is reflection of the different methods countries use to manage price, make it difficult to have a consistent global pricing approach. Pricing needs to evolve to take into account the realities of the 21st Century where ‘pricing corridors’ no longer work. This will change value expectations, affordability, utility assessments, commitment to access, de-linking from health and industrial agenda. By default this will lead towards greater cross-border transparency, it will define new global pricing referencing and consequently it will change nature of innovation in a way it will shift towards small volume therapies, interclass referencing, lifestyle diagnostics etc.



Establishment of a common denominator with a clear ‘value proposition’ needs to be at the core of pricing and re-imbursement submissions. To optimise pricing across markets, development plans need to move from clinical claim vs. placebo and incorporate economic outcomes. Finally, incremental costs need to consider potential incremental revenues from

priority markets (price, positive formulary place, time-to-market) and the potential downside risk of unfavourable comparisons with alternative treatments. A long way to go but shorter if it starts today.

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Innovative Pharmaceutical Products in EU – is there any room for improvement?

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**THE INTRODUCTION OF THERAPEUTIC REFERENCE PRICING SYSTEM IN
SLOVENIA**

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In 2003, the Health Insurance Institute of Slovenia (ZZZS) introduced a reference pricing system (NPV) for interchangeable drugs. This is one of the most important systemic mechanisms to control expenditure on medicines. The others are control of maximum prices by the Agency for Medicines and ZZZS' agreements with pharmaceutical companies. In 2013, the therapeutic reference pricing system (TSZ) was introduced. It determines the same reference level for a therapeutic group of drugs with the same indication. Sub-groups based on dosage levels may be formed. In each group the reference active ingredient can be defined; if not defined, the reference level is always on the cheapest product. The reference active ingredient has to have a certain volume market share, defined by the formula: $100 / (n+1)$ (where n = the number of active ingredients). In case of four active ingredients, for example, the minimum share would be $100/5$ or 20 %. Furthermore, in order for a product (presentation) to be used as a reference product, it would need to account for at least 0,5 % share by volume (DDD) of its group or sub-group. For products with certain pharmaceutical or therapeutic properties, an added value may be defined and the reference level can be lifted. In the same group, a limited range of prices may be created. Price ranges in many groups are large; they may be well over 100%.

In October 2013, first group with proton pump inhibitors was published. In 2014, lipid-lowering drugs (statins and ezetimibe) ACE inhibitors, acetylsalicylic acid and imatinib followed. New group will be regularly added and the existing ones periodically checked. Savings in each group are between 15 and 40 %. Most of the prices of medicines adjusted in the first month following introduction of each group. There are co-payments for less than 10 % of products in the groups. In case when replacement of medicines for medical reasons (i.e. side-effects) is not possible, a doctor may write on prescription: "do not substitute!" and a patient is exempted from the co-payment.

O.P. 28

**THE CURRENT PRICING AND REIMBURSEMENT SYSTEM FOR
PHARMACEUTICALS IN BULGARIA**

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Key words: reimbursement, medicinal products, pharmaceuticals, regulation, Bulgaria

Introduction: The pricing and reimbursement framework is an essential part of a pharmaceutical system. In the European Union (EU), Member States are free to develop their national pharmaceutical policies in the field of pricing and reimbursement as long as they comply with the general EU provisions – the Transparency Directive 89/105/EEC. The first positive reimbursement list (PDL) for pharmaceuticals was published in Bulgaria in 2003. The relevant regulation at that time required pharmacoeconomic analysis of the anticipated benefits of the treatment submitted for reimbursement but no detailed information regarding the template and the requirements of such analysis in the current legislation or in guidelines was given at that time. The regulation endorsed in 2008 unlike the previous one, focused on cost-effectiveness of pharmaceutical products submitted for reimbursement, and its budget impact. A new pricing and reimbursement regulation came into force in end of April last year 2014 in Bulgaria. It continues the line of amendments which started at the end of 2012 as a result of the heavy pressure to lower the prices of the medicinal products. In May 2012 the Bulgarian Parliament appointed the Bulgarian National Audit Office (BNAO) to audit the performance of the price regulation system for reimbursed medicinal products in the period January 2008 – December 2011. The report was published in November 2012 and one of the key conclusions was that the pricing and reimbursement administration process was extended and prevented the adequate market access of mainly new medicinal products and it was ineffective to systematically update the approved prices in case of referent prices decrease. As a result of these (BNAO) findings a new institution responsible for pricing and reimbursement of medicines was established in March 2013 – namely National Council of Pricing and Reimbursement of Medicinal Products (NCPRMP). The current publication analyses the effect on the pricing and reimbursement of the new legislation.

Results and discussion: Currently Bulgaria applies both medicinal product-specific eligibility and disease-specific eligibility schemes. There are reimbursement rates of 100%, 75%, 50% and 25%. Inclusion in positive drug list is based on the efficacy of the medicinal products, their cost-

effectiveness, existence of therapeutic alternative and their budget impact. De-listing is executed in case of lower therapeutic efficacy, excessive prices and switch to over-the-counter regimen.

The NCPRMP had 276 (accounting for 6% from all procedures in 2013) procedures transferred from the previous Commission on Pricing and Reimbursement which led to overload of the Council from the very beginning of its formation. For the observed period number of the assessed applications were 5287 where the majority of the submitted procedures (68%) concerned reference price comparison in 17 MSs in the EU based on official price reviews (performed every 6 months for each authorized MP).

The procedures for inclusion in PDL accounted for 24,9% from the submitted to the National Council procedures, while exclusion of MPs from reimbursement procedures were 5,3%. All inclusion procedures requested pharmacoeconomic analysis submitted by the companies, which was reviewed by the experts in the NCPRM. For the observed period 205 medicinal products were approved for reimbursement which includes 22 new INN which is serious scientific and administrative work. Exclusion of 140 MPs from reimbursement system were observed for different market and manufacture reasons. As a result in 2013 the prices of 842 medicinal products were reduced and the reduction of the prices per pack varies from 0.1% to 57.26% which led to substantial reduction of treatment costs.

Conclusion: The creation of National Council on Pricing & Reimbursement was a step forward as the single pricing and reimbursement administrative procedure cut down the overall procedural timeline. However, the reimbursement system in Bulgaria is facing several substantial challenges amongst which are lack of overall financial analysis of healthcare system and pharmaceutical policy; lack of legal environment for generic substitution of medicinal products and incentives for physicians to constrain the costs (or pharmaceutical budgets for doctors); lack of registries for patients with chronic diseases, etc.

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O.P. 29

PHARMACEUTICAL PARALLEL IMPORT IN THE REPUBLIC OF MACEDONIA

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Key words: parallel import, Republic of Macedonia, regulatory issues, economic effects

Introduction: The term “parallel” describes that the medicinal products (MPs) are imported via pathways that are *parallel* to the authorized ones (designated by manufacturer or its original supplier), as a rival channels that are active in the same time. Parallel imported MPs are not counterfeit medicines, but lawfully authorized MPs that generate a lot of benefits for patients and health insurance funds i.e. access to lower-prices versions of the same authorized MPs (1). “Parallel import (PI)” as a legal category was introduced in the pharmaceutical legislation in the Republic of Macedonia (RoM) in January 2012 and it showed its real economic, legal and marketing effects after October 2013, when the last amendments of the national Law on Medicinal Products and Medical Devices (2) were adopted. The purpose of this article is to present the concept of pharmaceutical parallel import in the RoM and to discuss the economic impact raised by it.

Materials and Methods: Primary, the legal basis and provisions of the actual national legislation that regulates PI was reviewed. For the analysis of the economic impact of parallel imported medicines, the data-base (Central Register of MPs) of the Ministry of Health was searched. Cost comparison was made, as a basic model, to explore the economic impact of PI.

Results and Discussion: With the actual pharmaceutical legislation, the RoM has adopted own PI policies and rules with respect to exhaustion of rights recognized in WTO TRIPS Agreement. Parallel importers have to hold a valid wholesaler and distribution license, manufacturing authorization for insertion a stick-label and a user leaflet (written in the official language), qualified person for pharmacovigilance and in a case of a product recall, a written agreement with licensed wholesaler from the exporting country. In addition, they should not be in commercial relation with the marketing authorization (MA) holder. National requirements do not allow any additional operations to be performed on the original packaging (e.g. repackaging into new contact container and/or external box). Such provisions are an adequate safeguard against counterfeiting, preventing from any infringement of the product reputation and damage of its origin. Within an approval process, the parallel importer must obtain a PI authorization, issued by the Bureau for MPs of the RoM. PI authorization can be granted if the imported medicine

meets the safety and quality standards and it is *significantly similar* to the authorized medicine in the RoM, thus being covered by the same authorization. Both products do not have to be identical in all aspects; at least, they should have same dosage form, same active ingredient in the same quantitative composition, same therapeutic effects, primary packaging with similar graphic package design and a common origin. Very important criterion is that both medicines should be produced by the same manufacturer/manufacturers that belong to the same group or should be produced under the license of the same licensed partner. Differences are possible, in composition of the non-active ingredients, production site and/or producer name, shelf-life/period of stability, and recommended indications; if they don't affect the quality, safety and/or efficacy. National provisions ensure and maintain safety of parallel imported medicines by permitting PI only for the MPs registered in the reference countries, with similar regulatory standards for MA. The procedure for obtaining PI authorization, quality control, responsibility of parallel importer in the process of vigilance and product recall in the supply chain are regulated by provisions that protect the public health. The implementation of PI policy in the RoM has started 6 months ago. Four domestic stakeholders showed interest for PI, primarily focused on branded MPs for hospital use. Several MPs obtained PI authorization and the number of applications increases. The first benefit from the PI was availability of the lower-price branded MPs, competition between wholesalers and price reduction of locally sourced products (Table 1). With multiple PI entrants in the last 6 months, the unique prices of the branded MPs have been reduced by 6,5 %. The effect of the marketplace and competition between branded and generic MPs was evident in a case of Imatinib, tabl. 400 mg. Namely, the PI of Glivec, tabl. 400 mg, decreased the unique price of the locally sourced branded MP by 4%, while the reduction in costs of hospital supply of this MP was 37%. However, the costs for hospital supply of the same generic drug, with market competition, have been reduced by 90%, suggesting that the generic / biosimilar penetration on the market might have additional impact on prices.

Table 1. Economic impact of PI on four parallel imported MPs in the RoM (source: Central Register of the Bureau for MPs, Ministry of health of the RoM)

| MP | Cost-savings with parallel imported MP (%) in public hospitals | Decrease in the unique price of the branded MPs with local MA (%) |
|-----------------------------|--|---|
| Eprex, amp. 4000 IU/0,4 ml | 33 | 8 |
| Sandostatin Lar, amp. 20 mg | 13 | 4 |
| Herceptin, amp. 150 mg | 17 | 0 |
| Glivec, tabl. 400 mg | 37 | 4 |

Conclusion: Pharmaceutical legislation in the RoM promotes the PI of MPs and with such a policy the both important goals are achieved, drug availability and moderation of the MPs prices. With this, a climate for foster competition between wholesalers is created, price reduction of locally sourced products, savings to patients/consumers and financial benefits for the health budget. The long-term impact of PI on MPs prices in all pharmacy settings (hospital as well as community pharmacies) still has to be determined.

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O.P. 30

**METHODOLOGY FOR THE MANNER OF CREATING PRICES OF MEDICINES IN
REPUBLIC OF MACEDONIA**

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Key words: reference countries, comparable wholesale price, average comparable wholesale price, and maximum wholesale price

Introduction: According to the Law of medicines and medical devices (Official Gazette of R.M 106/07), for the first time the new system of pricing of all prescribed medicines was introduced by the Ministry of health. As a result of breakdown of state pharmaceutical chain of pharmacies, establishment of unique retail prices of all medicines under prescription was necessary in order to keep the balance and to support the system of 760 licensed private pharmacies that were economically threatened from the existing large chains of pharmacies. In parallel this was needed to further protect the patients from variation of prices for same medicines. It was unavoidable that these changes had provoked a reaction by the number of suppliers and traders. Bureau of medicines regulated the prices of all 2.700 registered medicines placed on the market in Republic of Macedonia on three levels: unique wholesale price, unique retail price and defined wholesale and retail mark ups for all pharmacies and health institutions. Till 30.11.2011 wholesale and retail prices of all medicines under prescription were form only according to Article 108 of the Law of medicines and medical devices as a sum from the following elements; Manufacturer's price; Wholesale mark-up and; Retail mark-up. In November 2011 Government of the Republic of Macedonia adopted the new Methodology for forming the prices of medicines. This methodology, although is not fully cost based methodology, provides a unique and general approach to the manner of establishment of medication prices.

Results and discussion: The wholesale and retail sale prices of medicines are established on the basis of a comparative wholesale price of the specific medicine in the countries of reference. Reference countries are the countries whose wholesale prices of drugs are being used for comparison with the wholesale prices of the drugs in the Republic of Macedonia as follows: Slovenia, Bulgaria, Netherlands, Poland, United Kingdom, France, Croatia, Serbia, Greece, Germany, Turkey and the Russian Federation. They have been chosen as reference, according to the large number of registered medicines placed on their markets.

For each pharmaceutical formulation both from generic category or originator and innovative category, twice a year Bureau of medicines creates and publish maximum wholesale price. The maximum wholesale price is an average comparable wholesale price of those medicines according to analyzes of the comparable wholesale prices of that formulation in reference countries. The comparable wholesale price in the reference countries according to Article 4, paragraph 2 of the Methodology is the wholesale price of the identical medicine (it has the same international nonproprietary name (INN), same pharmaceutical formulation, strength and packaging) in the reference countries. The comparable wholesale price is established for each pharmaceutical formulation, strength and packaging, respectively. If there is no drug of the same pharmaceutical formulation in the reference countries, a drug may be compared to a kindred formulation (for example: tablet – coated tablet – capsule or suspension – syrup – solution), whereas the formulations of drugs with extended or modified effects can not be recognized as the ones that do not have the same effect. In the event of a different number of packaged dosage units of the drug, the package that contains a comparable number of units i.e. the package that is the closest to the required one shall be used. In this case the comparable wholesale price is calculated as a comparable wholesale price per unit, calculated per number of units of the product. The comparable wholesale price for originator and innovative drugs is the average value of the two lowest comparable wholesale prices of the originator or innovative medicine of the same producer in the reference countries, and that shall be the maximum wholesale price of that originator or innovative medicine in the Republic of Macedonia. Mark-ups of the retail sales price of medicines is strictly defined according to this Methodology, and depends of the amount of the wholesale price. First revision of prices according to this methodology in February 2012 produced significant results with decrease of prices of 1025 generic medicines from 2178 medicines placed on the market in R.M, and 570 medicines originators and innovative from 766 placed on the market. The average decrement was 28, 13% at generic medicines and 34, 72% at originators and innovative medicines. The total saving for the HIF is estimated at 17,000, 000 Euros. The most common decreased generic medicines during these four revisions of prices in 2012 and 2013 are anti cancer medicines (up to 85,65%), antiviral medicines (up to 70,42%), cardiovascular medicines (up to 70,02%), CNS medicines (up to 68,90%), immunosuppressive medicines (up to 65,82%), anti lipoid medicines (up to 61,05%), anti inflammatory medicines (up to 55,37%). It is expected that this “release” of funds as results from the price reduction, will be shifted towards better generic and innovative drugs that will find a place by pharmacoeconomic analysis in the new positive list of drugs.

Conclusion: Pricing methodology gives a wide view of wholesale and retail prices of medicines in the region and in Europe. More than 1500 generic medicines and almost all originators were drastically decreased according to this Methodology during these three years which brought savings both to Health Insurance Fund, Public hospitals, and patients as well. However, it is noticeable that the process for price optimization will continue, but it will be focused on

implementation of pharmacoeconomic studies and evaluation methodology. Ultimate beneficiaries of this new approach will be the patients.

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O.P. 31

**COMPARISON OF EFFICACY AND COST OF ANTIHYPERTENSIVE THERAPY
WITH FIXED-DOSE COMBINATION VERSUS FREE-DRUG COMBINATION**

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Key words: fixed-dose combination, free-drug combination, antihypertensive therapy, adherence, cost

Introduction: Patients' adherence and persistence with pharmacotherapy is crucial for the successful treatment of hypertension. The majority of hypertensive patients are likely to require multiple-drug therapy in order to reach blood pressure targets, so fixed-dose combination of different drugs may help to increase patients' compliance and persistence in these cases. Multiple analyses have clearly demonstrated that a lack of adherence and/or persistence significantly increases the risk of cardiovascular events, emergency department visits, and hospitalization. Our goal was to compare the effectiveness and cost of the therapy with fixed-dose combination versus free-drug combination. Our analysis included 202 patients from pharmacy in Kaštel Sućurac (104 patients on therapy with fixed-dose combination and 98 on therapy with free-drug combination). In spite of the fact that the most used fixed-combination was ramipril/hydrochlorothiazide (in 31% of patients), in our analysis we compared fixed-dose combination of perindopril and indapamide 5/1.25 mg with free-drug combination of same drugs because hydrochlorothiazide as a single component is not available in Croatia. The cost of fixed-dose combination was 0.90 HRK per tablet and the cost of free-drug combination 1.30 HRK per tablet.

Results and discussion: The results of our analysis showed that average blood pressure level with fixed-dose combination was $149.2 \pm 17.9 / 86.2 \pm 8.5$ mmHg and with free-drug combination $156.7 \pm 18.9 / 88.4 \pm 11.8$ mmHg. The target blood pressure level $<140/90$ mmHg was achieved in 37.2% patients treated with fixed-dose combination compared with 16.3% patients on free-drug combination. The cost of monthly therapy with fixed-dose combination was 27 HRK and with free-drug combination 39 HRK.

Conclusion: Patients who receive fixed-dose combinations have been shown to be more likely to achieve BP goal compared with patients who receive free-drug combination therapy. Our results

show that fixed-dose combination is more effective in lowering blood pressure than free-drug combination and at the same time less costly. In these patients, use of fixed-dose preparations simplifies the therapeutic regimen and has been shown to improve adherence and persistence. Consequently, use of fixed-dose combinations rather than free-drug combinations in patients with hypertension may be both clinically and economically beneficial. It could be concluded that fixed-dose combination should be preferred option in the pharmacotherapy of hypertension.

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O.P.32

COST EFFECTIVENESS OF FOSFOMYCIN USE FOR UNCOMPLICATED URINARY TRACT INFECTIONS CAUSED BY MICROBIAL STRAINS PRODUCING EXTENDED SPECTRUM BETA-LACTAMASES

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Key words: ESBL, UTI, urinary tract infection, fosfomycin, cost effectiveness analysis

Introduction: Antimicrobial Availability Task Force (AATF) in 2006 identified 6 most important multiresistant microbial pathogens: *Acinetobacter baumannii*, *Aspergillus* spp., Enterobacteriaceae producing extended spectrum betalactamases (ESBL), vancomycin resistant *Enterococcus*, MRSA and *P. aeruginosa*. Fosfomycin is an antibiotic that inactivates enolpyruvyl transferase, thus blocking condensation of uridine diphosphate- N-acetylglucosamine with phosphoenopyruvate and inhibiting bacterial cell wall synthesis. Standard therapy of urinary tract infections (UTI) caused by ESBL producing pathogens (38% of *Kl. pneumoniae* and 7% of *E. coli* hospital urinary isolates in Clinical Hospital Centre Zagreb in 2013.) relies on i.v. administration of carbapenem antibiotics (ertapenem, meropenem, imipenem + cilastatin, doripenem). In contrast, fosfomycin is given orally, in a single dose for uncomplicated urinary tract infections. It is well tolerated, *in vitro* resistance of common urinary pathogens as well as of ESBL producing strains is low and there is no cross resistance.

Results and discussion: Cost of 3 day course of carbapenem therapy of ESBL strain caused UTI can be projected as follows: ertapenem (140 €), meropenem (157€), imipenem+cilastatin (157€). If fosfomycin would be used, the projected cost for 1 day of therapy would be 10€ and 28€ for 3 day therapy (given as one dose every other day for 6 days), where longer administration is expected to increase effectiveness in comparison with single day fosfomycin regimen.

Conclusion: With reported therapy success rates between 80% and 95%, which is comparable to carbapenems, fosfomycin represents an extremely cost effective therapeutic option for uncomplicated UTI caused by ESBL producing strains.

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O.P. 33

NEW TREATMENT APPROACHES IN MULTIPLE MYELOMA PATIENTS - NEW DRUG, NEW PRICE, AND NEW QUALITY OF LIFE. WHAT DO WE GAIN?

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Multiple myeloma is still an incurable disease with pattern of regression and remission followed by multiple relapses raising from the residual myeloma cells surviving even in the patients who achieve complete clinical response to treatment. New anti-myeloma drugs change treatment paradigm providing both tumor reduction and tumor suppression. Today, multiple myeloma reminds of a bride with a story of something old, something new, something borrowed; something blue.....There is so much progress, but still many unsolved questions. In the mode of sequencing treatment for patients with multiple myeloma we are still using old drug such is the alkylating agent melphalan, which plays the role in an autologous transplantation as the only drug which attack myeloma stem cell. There are a lot of new drugs rising on the treatment scene like the monoclonal antibodies, histone deacetylases, new oral proteasome inhibitor, carfilzomib. We treated the patients with a borrowed concept, previously created for other hematological malignancies, consisting of induction, transplantation, maintenance. Allogeneic transplantation still reminds us of something blue.

The efficacy of treatment is mainly related to the achievement of a durable response. The goal of induction therapy is to achieve a maximum degree of tumor reduction before stem cell harvestation and transplantation. The achievement of a complete response (CR) is associated with prolongation of progression, free survival and overall survival. There are several randomized studies that enable physicians to choose the best regimen for initial therapy on the grounds of evidence based medicine. There are at least five classes of medications for the treatment of multiple myeloma: alkylators, corticosteroids, proteasome inhibitors, immunomodulatory drugs, and anthracyclines. All these drugs possess significant activity against multiple myeloma when used alone, but having in mind that they're mechanisms of action are complementary, their activity is increased further when they are combined accordingly between each-other. So, today we are facing numerous doublet, triplet and quadruplet combinations which have been tested through the use of these drugs.

Today, physicians are able to offer wider variety of treatment options for both young and elderly patients with multiple myeloma. Therapeutic options should be tailored and personalized according to patient's characteristics by balancing efficacy and toxicity of each drug. Effective treatment should be concentrated at the early phase of disease, when clones are more drug

sensitive, long – lasting remission are more frequent, and serious adverse events are less prominent. This approach significantly improves quality of life and may ultimately prolong overall survival.

O.P. 34

**POTENTIALLY INAPPROPRIATE PRESCRIBING IDENTIFIED BY TWO
DIFFERENT TOOLS AND HEALTH OUTCOMES ASSESSMENT**

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Key words: potentially inappropriate prescribing, Beers criteria, STOPP-START, health outcomes

Introduction: Elderly patients are at increased risk of adverse clinical outcomes such as hospitalization, falls, disability and mortality, directly involving increased consumption of health and social resources, being responsible for 70% of the pharmaceutical expenditure. The use of inappropriate medications is a major contributor to the risk of adverse events, especially in polymedicated patients aged 65 years old or more. Therefore, optimization of prescribing for this group of patients has become a major public health problem worldwide; the implementation and evaluation of screening tools is still needed to optimize the appropriate use of medicines.

There is growing interest in finding mechanisms to define the adequacy of pharmacological treatments and develop protocols for screening of potentially inappropriate prescriptions (PIP) in the past two decades. Two types of methods are being used - implicit and explicit. Among the most used, there are Beers criteria and STOPP-START. Beers criteria have dominated the international geriatric literature since they were first described in 1991. They have subsequently been modified to facilitate their use in people living in the community and were revised in 1997, 2003 and 2012. STOPP-START criteria were first created in Ireland and their clinical development has been undertaken by the Society of Geriatric Medicine of the European Union. These criteria, organized by physiological systems, list the most common treatment errors and omissions in prescribing and are easy to relate to active diagnostics and the list of drugs that appear in computerized medical records of patients.

The objective of our study was to evaluate the association between potentially inappropriate prescribing and health outcomes (specifically mortality, number of hospitalizations, domiciliary visits and emergency care) in an older people population at hospital discharge using two different tools for PIP detection (Beers and STOPP-START).

The study population was patients hospitalized in the University Specialty Hospital of San Cecilio, Granada, Spain during 2011-2012 and the average follow up period was 415 days.

Results and discussion

624 patients were included in the study, 55% women, with a mean age of 77.7 years (+ / -6.86 years). The patients had a Charlson Index average of 3.22. The average number of drugs prescribed at discharge was 8.55, with 47.92% of patients receiving more than 8 prescription drugs. The most frequently prescribed drugs at hospital discharge were Proton Pump Inhibitors in 72% of patients, followed by loop diuretics (44%), aspirin (33%), and beta-blockers (30%). A high frequency of prescribing was also observed for NSAIDs, warfarin, thiazide diuretics, oral and inhaled corticosteroids. The drugs most frequently listed as inappropriate using Beers criteria were alpha blockers, NSAIDs, and calcium antagonists; using STOPP criteria, aspirin and NSAIDs predominated.

Among the events detected during monitoring stands out the frequency of hospital readmissions within 30 days after discharge, which is higher for patients without PIP ($p = 0.053$) and an increase in the mean of domiciliary visits (43.7 versus 29.7) in patients with PIP, almost significantly.

Table 1. Effect of PIP on mortality after hospital discharge

| | cOR | CI | aOR | CI |
|-------------------------|------|-----------|------|-----------|
| Gender (ref. men) | 1.10 | 0.73-1.67 | 1.04 | 0.66-1.62 |
| Age (per year increase) | 1.04 | 1.01-1.07 | 1.04 | 1.00-1.07 |
| Charlson index | 1.42 | 1.24-1.63 | 1.42 | 1.23-1.64 |
| No. of drugs | 0.99 | 0.94-1.05 | 0.96 | 0.90-1.02 |
| Aspirin | 1.72 | 1.04-2.85 | 1.74 | 1.02-2.97 |

In Table 1, the effect of collected variables on mortality is analyzed. Association was found with age, representing 4% increase of the annual risk and with Charlson Index, with an increased mortality risk of 42% for each point increase. The possible effect of therapeutic drug groups classified as inappropriate by each set of criteria was assessed. We did not find any significant association for Beers criteria. Using STOPP-START criteria for PIP detection, a significant and independent increase in mortality was observed when aspirin was improperly prescribed, which was not verified when all aspirin prescriptions were analyzed.

Conclusion

Our results do not confirm the existence of a relationship between PIP measured by Beers or STOPP-START criteria and the use of health services in the medium term, although a significantly higher number of domiciliary visits is recorded. The inappropriate prescription of aspirin according to STOPP-START criteria behaved as an independent risk factor for mortality.

If we accept, as noted repeatedly in literature that the prescription of potentially inappropriate drugs is associated with increased healthcare costs and adverse events, and that this effect is preventable, it is truly essential to further identify and evaluate specific tools that can detect inappropriate prescribing. Acting on it might improve the safety of drug treatments, particularly among elderly patients with multiple pathologies.

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O.P. 35

**PHARMACOECONOMICS OF THE SHORT- TERM
PROPHYLAXIS OF THE HAE ATTACKS**

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Key words: Hereditary angioedema, short- term prophylaxis, C1 inhibitor, attenuated androgens, price

Introduction: Hereditary angioedema (HAE) is a rare disease with autosomal dominant inheritance, characterized by deficiency or dysfunction of C1 inhibitor (C1-INH). Typical clinical presentation includes recurrent angioedema, without urticaria and pruritus, that primarily affects the skin or the mucosal tissues of the upper respiratory and gastrointestinal tracts. Swelling may be self- limited, but laryngeal involvement can lead to airway obstruction and even death. The prevalence in general population is 1: 50 000.

There are 3 types of HAE. Type I HAE is characterized by low plasma levels of C1-INH protein. Type II HAE is characterized by normal to elevated C1- INH protein, but function is low. Type III HAE occurs mainly in women with normal functional and quantitative levels of C1-INH

Treatment approach consists of acute attacks therapy and prophylactic therapy.

Prophylactic therapy can be short- term and long- term. Short- term prophylaxis is indicated in situations that are recognized as triggers for attack, such as dental, oral and general surgery. Attenuated androgens are currently the initial mode of prophylactic treatment. Therapy should be minimized, balancing disease severity with minimizing adverse effects. The drug most commonly used is danazol, but all attenuated androgens are useful in treatment. The nano-filtered C1-INH concentrate is also labeled for short- term prophylaxis. The other options are antifibrinolytics and plasma products.

Discussion: There are few medications recognized as short- term prophylaxis of HAE attacks, with different mechanism of action, different adverse effects and different contraindications.

Assuming effectiveness and safety profile among approved short- term prophylaxis reasonable options would be attenuated androgens and C1- inhibitor.

There are no head- to- head randomized clinical trials comparing these medications.

On the other hand, no one of these medications provides 100 % protection of HAE attacks.

The price of therapy is also very important factor in making decisions, and big differences are presented in the table 1.

Table 1.

| | | | |
|---|-------------|----------------|---|
| Danazol | 600 mg/ day | Approx. 5 € | 5 days before and 5 days after surgery |
| C1 inhibitor (Berinert)* | 1500 IU | Approx. 4730 € | preferably within the hour before the procedure |
| Nanofiltered C1 inhibitor (Cinryze) | 1000 IU | Approx. 2000 € | preferably within the hour before the procedure |

*off- label use

In making decision process which short-term prophylaxis medication to chose, it is important to know what kind of surgery (minor or major) will patient undergo, is she/he already taking a long- term prophylaxis and what medications approved for prophylaxis are currently available at the hospital pharmacy.

Conclusion: Decision making while prescribing short- term prophylaxis should be pointed on the patient benefit considering all the facts about patient, procedure that patient will undergo and of course his prior experience with similar situations and prophylaxis if that one has already been taken.

On the other hand, the question is also the price of these medications. That fact largely influence their affordability.

Besides that, if the medicine is expensive and not the standard therapy for numerous patients, should it be allways available at the hospital pharmacy. Or, maybe we can simply prescribe cheap, effective medicine as attenuated androgen is, whenever there are no contraindications.

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O.P.36

OUTSOURCING IN PHARMACEUTICAL INDUSTRY

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Key words: Outsourcing, Generic Drugs, Contract Research Organizations, Project Management

The pharmaceutical industry is facing continuous rapid changes of its business practice and implemented strategy necessary for survival in terms of severe competition on the global market. The need of decrement of growing costs in this scientific and highly specialized area forces the engaged parties to rationalize their business activities without compromising the already achieved level of quality of their products. In the field of pharmacy and biotechnology the outsourcing or the cooperation with contract research organizations has been evidenced as the most attractive method in favor of cost rationalization and optimal usage of resources available. The practice of engaging contract research organizations (CROs) has not been a novelty for the above mentioned industries, however it has been tremendously intensified during the last two decades. Using the services of the scientific and research, as well as of medical centers from the new market economies, the pharmaceutical companies managed to rationalize the usage of their own resources, to eliminate time-gaps and to provide maximal rationalization of the duration of certain phases, by which they provided significant cuts of their costs and expenses. On the market as contract research organizations can act contract scientific and research organizations, academic medical centers and university hospitals, analytical laboratory centers, associated management organizations and institutions specialized for a particular market segment.

Outsourcing has especially great importance for the pharmaceutical companies in the field of generic drug development. In the strategy of the pharmaceutical companies from the developed economies dominates the orientation of intensifying scientific research activities in the field of development of additional large number of new generics. These activities have been effectuated by implementing project management as practice performed by the contemporary business elite for decades. The project management applied in pharmacy is effectuated in five key steps: project definition, strategy creation, detailed planning, implementation and control and revision and learning. Including Central and Eastern European countries as full members of the EU, a part of the Balkan states, among which belongs our country as well, became attractive for conducting projects sponsored by pharmaceutical companies that originate from the EU. Being included in

this type of projects our institutions are able to achieve not only gains in terms of additional financial inflow, but also of knowledge transfer on standardization and management of the terminal phase of generic drugs development up to the adopted western standards and practices.

Up-to-date experience confirmed that also institutions of higher education in the western economies are able to comply with the role of single-window providers for different services for the needs of the pharmaceutical industry. Also, the Faculty of Medicine at the “Ss. Cyril and Methodius University” in Skopje has established a six-decade tradition of well developed system of cooperation with the domestic pharmaceutical industry. Lately it started to develop cooperation with foreign pharmaceutical companies, as well.

For the successful accomplishment of this kind of research it is necessary to fulfill the following preconditions: presence of highly qualified and professional personnel; thorough knowledge of the national and international legislation and regulation on generic drugs; established standard operation procedures as required for conducting project activities; excellent reputation on following dead lines up to the contract; quality project management and consulting role fulfillment; well-established infrastructure, capacity and technology under controlled working conditions; experience in performing different laboratory practices; quality data-management on contracted projects; reputation confirmed by cooperating clients' satisfaction; etc. The preparation and the conduct of the research is a multitasking process where activities should be performed by a precisely defined schedule and established criteria.

O.P. 37

Vlad Zah (Serbia) – Overview of ISPOR CEE Network

O.P. 38

IMPORTANCE OF ISPOR CEE NETWORK FOR MACEDONIA

Ljubica Shuturkova

President of ISPOR –Skopje, regional ISPOR chapter from Republic of Macedonia

ISPOR Regional Network was established in November 2012, within the organizational structure of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), which consists of ISPOR Regional Chapters from different countries, who share a common language or geographic location.

The Network represents Regional Chapter members interested in the science of pharmacoeconomics (health economics) and outcomes research which is used in health care policies and decisions. Namely, this Network serves as a resource at the regional level for researchers who specialize in pharmacoeconomics, patient health outcomes, as well as those interested in ways how science is used in health care decisions.

An ISPOR Network is composed of the Executive Committee and three Working Committees: Education Committee, Publication Committee and Research Committee. The Executive Committee is the governing body.

The main goals of the Network include the following:

- initiating and promoting quality educational opportunities on pharmacoeconomics and outcome research (clinical, economic and patient reported outcomes);
- organizing regional conferences, training activities and translation activities;
- collaborating on research proposals;

ISPOR CEE Network gives opportunities to all CEE members for collaboration in the field of pharmacoeconomy and outcomes. The importance of such activities for R. Macedonia as a low-income country is of immense significance. Being a member, we Regional Chapter can contribute in all activities of the Network and at the same time improve the effectiveness and efficiency of our health care system.

O.P. 39

Guanka Petrova (Bulgaria) – ISPOR CEE Network current situation for Bulgaria

O.P. 40

ISPOR CEE RESEARCH COMMITTEE PARTICIPATION FROM R.MACEDONIA

Ass.Prof. Zoran Sterjev

ISPOR –Skopje, regional ISPOR chapter from Republic of Macedonia

ISPOR CEE Network Research Committee is developed under the umbrella of ISPOR CEE Network. The Network Research Committee is formed to design and/or engage in projects that enhance the science of the pharmacoeconomics (health economics) and outcomes research (clinical, economic, and patient-reported outcomes) and lead to improvements in the health care system in the region. The Committee facilitates the development of ISPOR Global Health Care Systems Roadmap and provides updates to ISPOR PE Guidelines (if applicable). The Regional ISPOR Chapter from Republic of Macedonia, ISPOR - Skopje participated in this network from 2013. In the previous period we have been included in some activity of the Research Committee like: Development of ISPOR Global Health Care Systems Roadmap and International Price Referencing Survey in Central-Eastern European Middle – Income Countries. As the members of ISPOR CEE Network Research Committee, we also received a list of preliminary research topics proposed by the Research Committee which will be developed into the Research Committee projects. This list covered 18 preliminary research topics. In accordance with our interest in the offered topics, we decided to join eight of these research topics. Each one of the registered experts for the individual proposed research topics was contacted by the ISPOR CEE research committee in order to express his/her opinion about the proposed issue, the expectations about the results from these projects and the timeline for implementation of the project. Another benefit for all of us professionals from CEE countries, is Value in Health Regional Issues (ViHRI) a new scientific journal of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Formation of CEE research network is a very important benefit for a small and low-income country such as Macedonia, which finds it difficult to share the same problems with highly developed European countries and therefore, requires different kinds of solutions. The CEE research network will allow researchers access to a vast domain of research, and thus will enable their inclusion and recognition in the wider international teams.

O.P. 41

Tarik Catic (Bosnia and Hercegovina) – ISPOR CEE educational activity and research projects in BiH

POSTERS¹

¹ The abstracts are presented as received by the corresponding authors. The Scientific Board of the Congress does not take any responsibility for the content of the presented papers.

P01

**ECONOMIC EVALUATION OF THE ESTRADIOL VALERATE/ DIENOGEST
THERAPY FOR THE TREATMENT OF HEAVY MENSTRUAL BLEEDING IN R.
MACEDONIA**

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Introduction: Combined oral contraceptives (COCs) are generally used as off-label therapy in the treatment of heavy menstrual bleeding (HMB). Estradiol valerate/ dienogest (E2V/DNG) is a new COC approved for treatment of HMB in women who have no organic pathology, and who want to receive oral contraception.

Objective: The aim of this study was to compare the costs and effectiveness of the E2V/DNG versus LNG-IUS in the first line treatment of HMB and to evaluate the economic viability of their use in R. Macedonia.

Method: A cost-effectiveness and cost-utility analysis was carried out. A decision tree model of first line E2V/DNG compared to first line LNG-IUS was constructed for patients diagnosed with idiopathic menorrhagia. Clinical data from the Lete et al. 2011, trial were used to replicate the effectiveness of LNG-IUS and COCs in a time horizon of 5 years. Only direct costs relating to the HMB drug therapy are included in the analysis. The utility estimates of the medical treatments, measured as quality-adjusted life months (QALMs) were extracted from randomized clinical studies data. The analysis was performed from the National Health Care System perspective. The price per dose was then estimated, and cost per QALM with a 3% annual discount was calculated.

Results: A total accumulated cost per patient, for E2V/DNG vs. LNG-IUS, after one year of treatment, was 169.57 EUR versus 43.15 EUR, respectively. The incremental cost per QALM gained for LNG-IUS compared to E2V/DNG was 78.03 - 224.54 EUR, after 12 months-5 years.

Conclusion: Although, the costs associated with both therapies of choice justify their therapeutic outcome, E2V/DNG cannot be considered as the dominant option (less costly and more effective) in comparison with first-line use of LNG-IUS for the treatment of HMB in R. Macedonia.

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P02

**ANTIBACTERIALS CONSUMPTION IN THE AMBULATORY CARE REIMBURSED
BY HIF IN ALBANIA DURING 2013**

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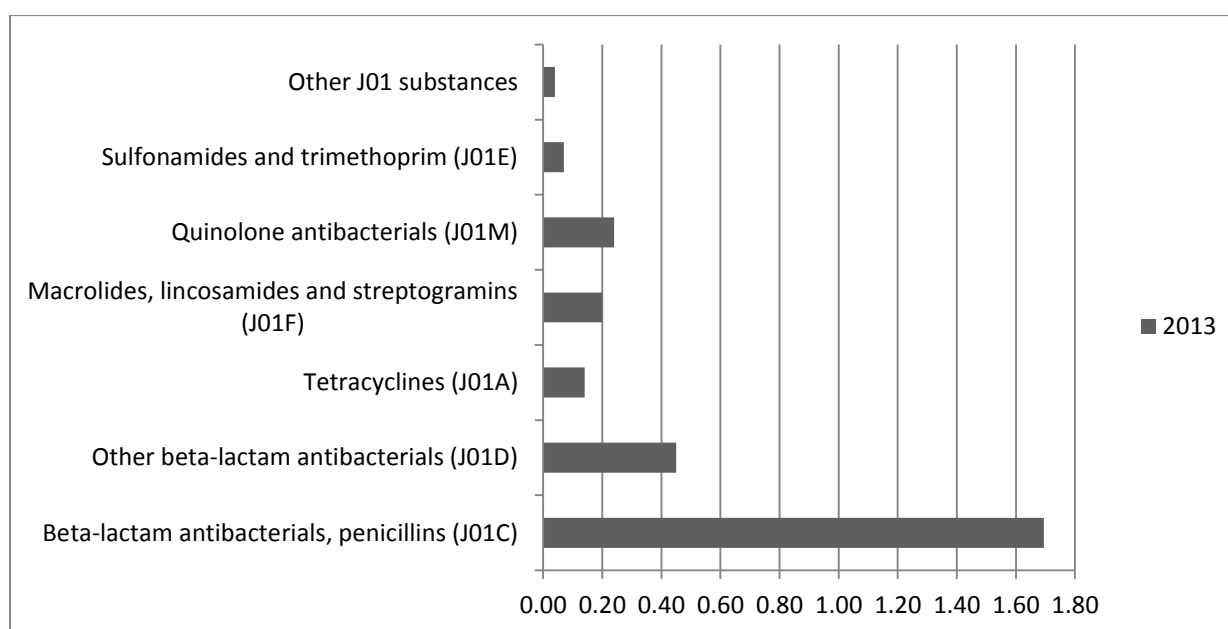
Key words: Antibacterial consumption, drug utilization, ambulatory care, Albania

Background: Emphasis on the misuse of antibacterials in Albania and an increased sensibility on the antibacterial resistance have been reported in the grey literature lately. The objective of this study is to assess the antibacterial utilization reimbursed by the Health Insurance Fond (HIF) (1) in the ambulatory care in Albania during 2013. Data from the HIF database for all the reimbursed and dispensed antibacterial in the ambulatory care were taken and the methodology of ATC/DDD (version 2014) (2) for the study of antibacterial utilization was applied. Antibacterial grouped in ATC class were measured in defines daily doses (DDD) and DDD/1000 inhabitant/day (DIDs) (3,4) and then compared with the data of the European Surveillance of Antimicrobial Consumption Network (ESAC-Net), latest report of 2011(5). Also the reimbursement data were compared with the reimbursement data of penicillin's and cephalosporin's during 2011-2012 (6,7) and also with the latest reimbursement list of 2014 in order to track the possible changes in the reimbursement scheme for antibacterials for systemic use (J01) in Albania.

Results and discussion: Results of the total consumption of antibacterials reimbursed by the HIF measured during 2013 are (2.98 DID). The penicillin's (J01C) total consumption in 2013 is (1.69 DID) which is the mostly used subgroup and its use slightly increased compared with the reimbursement data of 2012 (1.6 DID) The consumption shifts to the cephalosporin's subgroup with (0.45 DID), this subgroup increased significantly compared with 2012 reimbursement data (0.37 DID). Also, an enhancement of the use of second generation of cephalosporin's (J01DC) was distinguished within the class of cephalosporin's in 2013, (0.27 DID). Quinolones, macrolides and tetracycline's are the frequently subgroups used in 2013. Compared with the reimbursement drug list approved in 2014, only nitrofurantoin (J01XE01) was added to the reimbursement drug list 2014 and the rest of the J01C list contains the same subclasses with some alternatives removed or added in the subclasses. The quantities of antibacterial reimbursed for HIF covered population during 2013 are more lower than the average consumption of EU/EAA countries part of ESAC-Net as referred in the latest report (EU median 19.5DID)(5). The low consumption of reimbursed antibacterials may depend from several factors like the low use of insurance services or low access to these services from the covered population in

the ambulatory care. This could suggest that patients tend to consume out of pocket prescribed antibacterials and also bypass the treatment protocols, and also the insurance scheme.

Conclusions: Further studies on antibacterial regulation and protocols should be made in order to better assess these issues, because as we are sure that the treatment protocols used to prescribe reimbursed antibacterials refer to the standards approved by Ministry of Health, we are not sure that the out of pocket antibacterial prescription is in coherence with the treatment protocols, as suggested by a little survey made in Tirana(8). Studies on accessibility of reimbursed healthcare services, specifically ambulatorial one should be made. Also studies for the overall consumption have to be finalized by the working group.



Graph 1. Antibacterial consumption reimbursed by HIF during 2013.

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P03

**FINANCIAL ANALYSIS OF THE COST OF RARE DISEASES PHARMACOTHERAPY
IN BULGARIA**

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Key words: rare diseases, pharmacotherapy cost, financial analysis

Introduction: This study presents the results of the analysis of financial performance of pharmacotherapy for rare diseases from the perspective of the payer (NHIF) in Bulgaria. Key points of this study are the proportion of funds allocated for rare diseases as part of the cost of drugs and GNP of the country; type of resource-intensive diseases and medicines; trends in financing the treatment of rare diseases and orphan drugs in our country.

Materials and methods: It is a macro costing, retrospective incidence cost study for the period 2010 to 2013. From the National health insurance fund on central and regional level was collected and analyzed the reimbursement of medicinal products, medical devices and dietary foods for special purposes, number of diagnoses of rare diseases financed by the Fund (ICD), and number of patients. The medicines are grouped by INN and therapeutic class. Regressive correlation models were built to forecast the future medicines expenses till 2016.

Results and discussion: The number of patients, as the budget allocated to orphan drugs, increased over time, as critical is the transfer of cancer drugs to the NHIF. Expenses for rare diseases account for no more than 10% of that cost due to regulatory restrictions. Regional budget data also show that pharmacotherapy of rare diseases require significant financial resources, with great variations in small regions (Figure 1).

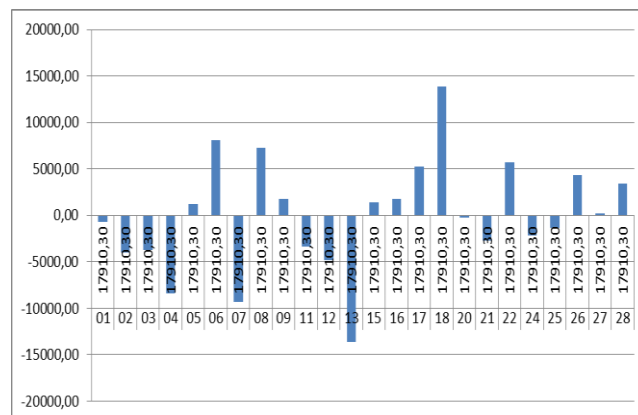


Figure 1. Regional cost differences for patients with thalassemia

So care is needed to provide the necessary resources to enable more patients to be treated with advanced therapy without straining the limited public funds. In 2013 the expenditures for pharmaceuticals for RD were included into the total health care budget and were not reported separately. The expenditures for oncology medicines were added, due to the fact that their financial responsibility was transferred to the NHIF from the Ministry of health (Table 1).

Table 1. The structure of the NHIF medicines expenditures during 2010-2013 (mill €)

| | 2010 | 2011 | 2012 | 2013 |
|---|------|------|------|------|
| Expenditures for medicines, medical devices, and special foods. | 197 | 242 | 265 | 274 |
| Expenditures for medicines | 187 | 231 | 255 | 263 |
| Expenditures for orphan medicines for rare disease therapy | | 20 | 20 | 27 |

It is evident that there is a substantial growth in the health care expenditures for pharmaceuticals, including the RD therapy and all the changes in expenditures are statistically significant ($p < 0.05$). The increase in the expenditures is a consequence of not only the changes in budget policy, but also of the changes in the number of the reimbursed diagnoses and medicines which are constantly increasing. The reimbursed sum for medicines for rare diseases follows a linear regression curve. The mathematical model is based on a linear regression model, built from existing data regarding the reimbursed sums by the NHIF for rare disease, with a base year 1 =

2011 and subsequent 2 = 2012 и 3 = 2013, all shown on the x-axis. The regression equation, which describes the model, is as follows:

$$\text{Reimbursed sum} = 15\,430\,000 + 13\,520\,000 \times \text{year}$$

Correlation coefficient $R = 0.999$; Coefficient of determination $R^2 = 0.998$ $F = 613.099$, $p = 0.026$ – This coefficient shows the extremely high adequacy of the model. If the current tendencies continue, the expected value for the sums reimbursed by the NHIF will be in the vicinity of 96,5 million BGN for the next three years (Table 2).

Table 2. Prognosis for the reimbursed sum for pharmacotherapy of rare diseases

| Year sequence number | Year | Reimbursed sum (mill BGN) | Expected sum (mill BGN) |
|----------------------|--------|----------------------------|--------------------------|
| 1 - base | 2011г. | 28,629 | 28,950 |
| 2 | 2012г. | 43,092 | 42,470 |
| 3 | 2013г. | 55,665 | 55,990 |
| 4 | 2014г. | | 69,510 |
| 5 | 2015г. | | 83,030 |
| 6 | 2016г. | | 96,550 |

Conclusion: Within the framework of the very dynamic regulatory environment and extensive scientific work in the field of rare diseases therapy the financial resources remain extremely limited to ensure appropriate therapy and scientifically based treatment. There is a need of collaboration on a European level and the creation of a global fund to be able to satisfy therapeutic needs.

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P04

**COST MINIMIZATION ANALYSIS OF TRASTUZUMAB SC VS. TRASTUZUMAB IV
FORMULATION IN PATIENTS WITH EARLY BREAST CANCER IN REPUBLIC OF
MACEDONIA**

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Key words: Trastuzumab, cost-minimization, breast cancer

Introduction: Breast cancer places a substantial economic burden on the whole society, patients and caregivers. According to last published data from 2012, for female cancer-related mortality in R.Macedonia, breast cancer is the leading cause, with mortality rate of 27.7 % per 100.000.¹ This puts R. Macedonia among the countries with the highest breast cancer mortality rate.² Trastuzumab is a humanized monoclonal antibody which selectively targets the human epidermal growth factor receptor (HER2).⁴ One-year adjuvant trastuzumab therapy increases disease-free and overall survival in the adjuvant treatment of early HER2-positive breast cancer.³ A cost-minimization analysis has been developed to compare the direct drug and non-drug costs associated with trastuzumab SC and trastuzumab IV. The analysis does not consider chemotherapy drug costs since these do not differ between the two formulations.⁴ This analysis comprehends non-drug related direct cost (IV lines, needles, infusion bags, cannules). Trastuzumab SC is provided in a ready-to-use, fixed dose vial, and is administered subcutaneously. Therefore, no reconstitution or weight-related dose adjustments are required, thus providing benefits in terms of equipment, resources and time required. Trastuzumab IV formulation requires an initial loading dose, as well as dose adjustment for individual patient body weights. Such dose adjustment may be associated with drug wastage, increased resource time and potential dosing errors. HannaH (BO22227) is a pivotal phase III, randomized, open-label, international, multicentre study in patients with operable or locally advanced EBC. The study was designed to assess non-inferiority between trastuzumab SC and trastuzumab IV in terms of two co-primary endpoints: pharmacokinetics (PK) and efficacy (pathological complete response rate). Results from HannaH show that trastuzumab SC provides comparable PK and efficacy to trastuzumab IV with non-inferiority demonstrated for both co-primary endpoints. Results also demonstrated comparable safety profiles which were consistent with the known safety profile of trastuzumab.⁵

Results and discussion: The cost-minimization analysis is a study in which two or more therapeutic alternatives with the same effectiveness or efficacy are compared in terms of net costs in order to establish the cheapest alternative. Since SC formulation of trastuzumab is

comparable to the IV formulation in terms of clinical efficacy and safety, a cost-minimization analysis was performed. The evaluation was considered from the perspective of Macedonia's Health Insurance Fund and includes only direct medical cost (drug and non-drug related). One year time frame was considered based on the treatment of early breast cancer; consequently a discount rate was not necessary. To conduct this evaluation the following parameters were considered: maximal price of both formulations on the basis of the Law on Medicines and Medical Devices and the Methodology on the Manner of Establishment of medication prices, which is also the referral (reimbursement) of the Health Insurance fund of Macedonia according last published prices from 28.01.2014.⁷ Consumption resources prices for trastuzumab IV application (IV lines, needles, infusion bags, and cannulas) are based on the last tender on medical devices and contracts published on Public Procurement Bureau.⁶ Since trastuzumab IV dosing is weight dependent mean weight of 70 kg was considered in the calculation. The calculations showed that total drug cost for the treatment per cycle per patient is lower for the SC formulation than for IV (101.928 MKD vs. 103.816 MKD). For all 18 cycles (1 year treatment) per patient also the SC drug cost is lower than the IV (1.834.704 MKD vs. 1.868.687 MKD). Considering non-drug related costs, i.e administration cost per cycle of the IV formulation of 4.140 MKD, the overall cost of trastuzumab IV per patient for all cycles is 1.872.827 MKD. Prices are excluding VAT. No discounting rate was applied since the time frame considered was 1 year. Results from the analysis showed that for a full course of treatment and assuming no drug wastage for trastuzumab IV, as it is the current practice, the use of trastuzumab SC results in a drug cost saving of 1.8% of the trastuzumab IV cost, if patients are treated with trastuzumab SC instead of trastuzumab IV. One-way sensitivity analysis was performed to understand the key drivers and general sensitivity of the model. The following variables were assessed: cost of the drug, both formulations and the mean weight of the patients.

Conclusion: The results of this study suggest that routine use of trastuzumab SC instead of trastuzumab IV has the potential to reduce the cost of treatment of 38.123 MKD per patient. Also if adding the saved time when using the SC formulation (e.g. staff time for infusion, preparation in pharmacy, preparation of patient for infusion, administration, chair time, and total time required for the patient in the hospital) the benefits are immense.

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P05

**UTILIZATION OF HEPARIN AND LOW MOLECULAR WEIGHT HEPARINS AT
THE ORTHOPEDIC DEPARTMENT AT THE CLINICAL HOSPITAL IN STIP**

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Background: A number of cost drivers that contribute to the rising specialty drug spend have been identified within the managed care infrastructure. Among these cost drivers are drug mix, the degree of provider reimbursement, member benefit design, distribution channel, the extent of utilization management, and the degree of operational effectiveness in paying claims correctly.

Objectives: The main goal of our study was the comparison of the utilization of heparin and low molecular weight heparins at the orthopedic department at the Clinical Hospital in Stip, along with the required quantities of the drugs for the Orthopedic Department needs, in the 2013 year. Through this comparison, we wanted to see whether the established way of requisition correspond with the actual utilization, or it generates unrealistic charges imposing the need of introducing system for internal requisition of the medicines in our hospital.

Methods: In order to realize this goal, the review of the medical records of a total of 1087 registered patients from the orthopedic department at the Clinical Hospital – Stip was made, during 2013 year. Data for utilization of analyzed drugs are compared with the official data for the required heparin and low molecular weight heparins, from the Orthopedic Department at the Clinical Hospital in Stip.

Results: During their treatment, 423 patients from the total number of registered patients received heparin or its low molecular derivatives. 223 patients of these were treated with heparin, 164 patients were on low molecular weight heparin preparations, and 36 patients were on combined therapy of heparin and low molecular weight heparins. Administered dose and duration of therapy of these two classes of drugs were different, depending on individual characteristics and diagnosis of patients. The average daily dose of administered heparin was 10 000 IU, while the average daily dose of low molecular weight heparin was 4000 IU which is consistent with the therapeutic guidelines for the treatment of patients with these diseases. The requisition of the total amount of the required heparin for the needs of the Orthopedic

Department at the Clinical Hospital in Stip in 2013 was 23 725 000 IU/ 198810,55 MKD which according to the achieved prices for this period it amounted 65 000 IU / 544,69 MKD per day. The requisition of the total amount of the low molecular weight heparins for the purposes of the Orthopedic Department at the Clinical Hospital in Stip in 2013 was 7 108 850 IU/ 243599,56 MKD which according to the achieved prices for this period it amounted 19 476 IU/ 667,4 MKD per day. According to the evaluated data from the hospital patient records, the total consumption of heparin at the Orthopedic Department was 23 330 000 IU/ 195 500,53 MKD, while the total amount of low molecular weight heparin was 6434 150 IU/ 229 099,48 MKD . Expressed in monetary units, the difference between the requisition quantity and real consumed quantity of heparin amounted 3310,02 MKD, while for the low molecular weight heparin it is 14500,08 MKD.

Conclusion: The recorded results suggest that the current method of requisition of drugs, based on the daily needs of patients is irrational and it generates the costs in the operation of the Clinical Hospital. To overcome this problem, it is necessary of introduction the new health technologies, such as bar coding of distribution of medicines, as an investment that has been shown to be cost-effective in a number of healthcare centers in the world. Anyway, before taking such a step, it is necessary to make all investigations into the cost-effectiveness of the introduction of the new technology.

P06

**MARKET ENTRY OF INNOVATIVE MEDICINES IN THE REPUBLIC OF
MACEDONIA**

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Key words: Innovative medicines, market entry, national legislation, medicines prices

Introduction: The competition between innovative and generic pharmaceutical companies intensified in the last decades. The models created by innovative pharmaceutical industries rest on market exclusivity, higher medicines prices and patent protection system. Republic of Macedonia has a limited medicines budget, and its healthcare policies aim to save on medicines supplies. The legislation in the Republic of Macedonia is constantly modified due to the harmonisation with the European regulation. The country intends to allow the entry and use of innovative medicines, especially for first- and second-line therapy. In this study, we aim to analyze the current legislation (legal acts, bylaws, price methodology) and describe the circumstances that lead to innovative medicines' market entry.

Results and discussion: National regulations were put in place to accelerate the access to innovative medicines, but their frequent adjustments according to all interested parties have delayed the process of efficient implementation. The 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 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 beneficial to the market offer, competition and medicines prices, but hampers the financial sustainability of the innovative companies.. The discontinued legal procedures 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 resources to be used to include new medicines in health care, but lower prices decrease the innovative companies' interest to enter the Macedonian market. Table 1 illustrates requests to include innovative medicines on the positive list. Only Imatinib was put on the positive list i 2011, including 3 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.

Conclusions: 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. The inclusion of expensive innovative medicines should be based on scientific evidence on drug efficiency, 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.

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P07

**USE OF ADULT FORMULATIONS IN CHILDREN: EVALUATION OF SPLITTING
 TABLETS OF RANITIDINE HYDROCHLORIDE**

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Key words: splitting tablets, pediatric formulations, score, ranitidine

Introduction: Many drugs administered to children are not available in formulations for pediatric use. Most marketed oral medicines are intended for adults and are solid dosage forms. Solid dosage forms present problems as children have difficulty swallowing whole tablets (TBL). Sometimes TBL are cut into smaller parts to obtain appropriate units for children. The purpose of this study was to evaluate accuracy of splitting ranitidine hydrochloride 150 mg TBL, in dosage for children. Ranitidine oral is used for the treatment of gastric/duodenal ulcer and GERD for both neonates and children, in respective dosage 1.5-2mg/kg/24h, q12h and 1-5mg/kg/24h, q6-8h (Bebeçi, 2006). The study was made with ranitidine hydrochloride 150 mg TBL, from 3 different manufacturers present in Albanian market. Products have been chosen based on the presence or not of the score line: scored on one side (S), scored on both sides (BS) and not scored (NS). Of each product, 100 TBL were taken at random and weighed, and mean weight (MW) was calculated. Then the TBL were divided into halves and quarters by using a pill-splitter. From each TBL one half and one quarter was weighed and mean weight was calculated. The range of 85% to 115% and 75% to 125% confidence intervals (CI) was determined based on the mean weight. For the whole TBL, halves and quarters, the weight deviation from the average weight was compared to the above interval.

Results and discussion: From the study were found that all the whole TBL were conform to the Eur.Pharm mass uniformity requirements. And only halves from S and BS tablets complied with the Eur.Pharm. 37% of halves from NS tablets deviated more the 15% from the mean (Table 1).

Table 1: Percentage of halves, that weight falls in the CI.

| Deviation from MW | % of halves fall in CI | | |
|-------------------|------------------------|-----|----|
| | S | BS | NS |
| X < 15% | 100 | 100 | 63 |

| | | | |
|----------------------|---|---|----|
| $15\% \leq X < 25\%$ | 0 | 0 | 29 |
| $25\% \leq X$ | 0 | 0 | 8 |

The results were worse with quarters. None of the quarters from evaluated products complied with Eur. Pharm requirements. Only 73% of quarters from S and BS tablets and 62% of quarter from NS tablets were within the CI of 15% (Table 2).

Table 2: Percentage of quarters, that weight falls in the CI.

| Deviation from MW | % of quarters fall in CI | | |
|----------------------|--------------------------|----|----|
| | S | BS | NS |
| $X < 15\%$ | 73 | 73 | 62 |
| $15\% \leq X < 25\%$ | 20 | 23 | 25 |
| $25\% \leq X$ | 7 | 4 | 13 |

Conclusion: By breaking Ranitidine TBL into halves and quarters were observed large deviations. These deviations were related to the presence or not of the score line. Such inadequate breaking of TBL may result in dose variability and complicate therapeutic outcome. In small markets where introduction of lower doses may not have commercial interest, appropriate scored TBL (scored both sides) can ensure more flexible dosage. There is a need for pediatric formulations and dose adaptation based to child body weight.

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P08

ECONOMIC EVALUATION OF ANTIBIOTIC PRESCRIPTIONS IN PEDIATRICS

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Key words: Pharmacoeconomics, cost minimization analysis, pediatrics, antibiotics

Introduction: “Pharmacoeconomics” is a new word; but economic interest in drug and other treatments of health problems is much older. Decisions about what treatments should be available within a health-care system have always been influenced by the resources available to pay for them. Pharmacoeconomic analysis should be the preferred tool for guiding antibacterial formulary decisions and evaluating the economic impact of antibacterial use because it is usually based on clinical outcomes and does not merely evaluate drug acquisition costs. Knowledge of pharmacoeconomics is therefore vital for doctors to promote rational prescribing. Cost Minimization Analysis (CMA) involves measuring only costs, and is applicable only when the health benefits obtained from two alternative therapies are identical and therefore need not be considered separately. For example, comparing the costs of two different brands of the same drug or comparing the cost of a branded drug with its generic form. The objective of the study was to perform a cost minimization analysis of antibiotic prescriptions in pediatric cases. This was a retrospective study performed in 3151 pediatric out-patients prescribed with antibiotics. The commonly prescribed antibiotics in this study were chosen as examples to illustrate the cost difference between the most expensive and the least expensive brand versions of the same antibiotic, expressed in denars. In evaluating them, the same dosage form, equal strength and the same frequency of dosing were considered. If only one brand was available for a drug without any competitor’s brand that particular drug was excluded. The prices were obtained from the official price list, put up by the Ministry of Health of Republic of Macedonia. The percentage variation in price was calculated and presented in the results section.

Results and discussion: Results for cost minimization analysis are given in Table 1. This table shows a summary of prescribed antibiotics, their frequency of prescription, costs and the percentage of price difference. Results indicated that the use of branded drugs which were more expensive was noticeable even when the cheaper options were available. The costliest brand of amoxicillin syrup prescribed in 277 (65.6%) patients, having a maximum retail price of 89.6 denars, was 33.7% costlier than the least expensive version (34.4%).

Table 1. Cost comparison between the most expensive and the least expensive brand versions of antibiotics

| Antibiotic | No. of prescriptions | Cost of most expensive brand in denars | Frequency of prescriptions | Cost of least expensive brand in denars | Frequency of prescriptions | % Of cost difference |
|-----------------------------|----------------------|--|----------------------------|---|----------------------------|----------------------|
| Amoxicillin Syrup 250 mg | 422 | 89.6 | 277 (65.6%) | 67 | 145 (34.4%) | 33.7 |
| Cefalexin Syrup 250 mg | 393 | 162.2 | 347 (88.3%) | 110.3 | 46 (11.7%) | 47.1 |
| Cefaclor Syrup 125 mg | 351 | 152.8 | 338 (96.3%) | 143.1 | 13 (3.7%) | 6.8 |
| Cefaclor Syrup 250 mg | 42 | 241 | 32 (76.2%) | 201.8 | 10 (23.8%) | 19.4 |
| Cefadroxi 1 Syrup 250 mg | 287 | 307.1 | 111 (38.7%) | 282.2 | 176 (61.3) | 8.8 |
| Cefadroxi 1 Capsules 250 mg | 15 | 433.3 | 7 (46.7%) | 329.2 | 8 (53.3%) | 31.6 |

Among cephalosporins, cefalexin syrup was the most commonly prescribed. Its most expensive brand version was 47.1% costlier than the least expensive brand version. The most expensive brand was prescribed 347 times (88.3%) compared with the least expensive version prescribed only 46 times (11.7%). In case of cefaclor syrup 125 mg, the cost differences between the most and least expensive brands were 6.8%. The most expensive branded cefaclor was prescribed 338 (96.3%) compared with the least expensive version prescribed 13 times (3.7%). The cost difference between the most expensive brand of cefaclor syrup 250 prescribed 32 times (76.2%)

and least expensive brand prescribed 10 times (23.8%) was 19.4%. Cefadroxil syrup brand versions showed 8.8% cost difference, with higher percentage of prescribing toward the least expensive brand in 61.3% compared to the most expensive brand prescribed in 38.7% patients. The cost difference was higher when cefadroxil capsules 250 mg were prescribed (31.6%).

Conclusion: Antibiotics account for the highest proportion of the drug budget in many countries and constitute the largest group of drugs purchased. This cost minimization study has shown a presence of cost difference between the most expensive and least expensive brand versions of the same antibiotic. The cost of most expensive branded drugs prescribed was 6.8% to 47.1% more than the least expensive versions. This means that parents are spending much more on the treatment of their children than what is necessary. It is concluded that economic evaluation, such as cost minimization analysis is of paramount importance in policy and decision making to facilitate more rational choices and to reduce the financial burden on the patients.

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P09

EVIDENCE BASED MEDICAL CARE AND PHARMACOECONOMICS

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Key words: evidence based medical care, pharmacoeconomics, newborns, health care

An evidence-based practitioner must be able to understand the patient's circumstances, to identify knowledge gaps, and frame questions to fill those gaps; to conduct an efficient literature search; to critically appraise the research evidence, and to apply that evidence to patient care.¹ Delivering evidence-based medical care requires providing care that is high-quality and safe, and at the same time cost-effective. However, while the knowledge and technology regarding effective medical therapy continuously improves, the practice of medicine is not on the same level, because the risk of iatrogenic errors becomes higher.² Regarding the gaps between evidence and practice, Lomas et al.³ evaluated a series of published guidelines and found that it took an average of approximately five years for these guidelines to be adopted into routine practice. Pharmacoeconomics involves processes similar to EBM, but it deals with decisions on the population rather than the patient level. Pharmacoeconomics is the scientific discipline that evaluates the clinical, economic and humanistic aspects of pharmaceutical products, services, and programs, as well as other health care interventions to provide health care decision makers, providers and patients with valuable information for optimal outcomes and the allocation of health care resources. The overall goal of it is to provide the most efficient use of resources, taking into account both the cost and the value derived from a given technology. These evaluations assist health care decision making because both cost and effectiveness are considered. New therapies are increasingly complex in terms of administration, effects, and cost. At present, there is no standard threshold for what constitutes cost-effective therapy, so each health care system is likely to have its own criterion for acceptance. Taking into consideration the accelerated process of developing/adopting and adapting Clinical Guidelines based on high level of evidence, the aim of this paper was to evaluate the role of Evidence Based Medical Care in the context of pharmacoeconomic (PE) decision making by health care providers. Clinical Guidelines may be considered a measure for providing evidence-based care, increasing the patient safety and reducing the unnecessary costs, thus improving the cost/benefit ratio. The method of evaluation consisted of the following steps: deep review process of the two most frequent clinical disturbances (neonatal non-haemolytic jaundice and early onset infection) in term newborns born at the University Clinic for Gynecology and Obstetrics in Skopje, detailed analysis of the nationally accepted Clinical evidence based guidelines covering the same

diseases, and performing comparative analysis of the number and type of investigations in two time-periods-before and after implementation of the Guidelines.

Results: throughout the evaluation, many of the previously explored investigations and therapy introduced, were found unnecessary. Within the first clinical disease-non-haemolytic jaundice, using evidence-based Clinical guidelines enables the clinician to reduce the number of venepunctures (by introducing the transcutaneous bilirubinometer and clinical application of the Kramer's rule), reduces the necessity for phototherapy (PT) by using the threshold levels of the serum bilirubin for PT for separate gestational age and for exchange transfusion as well. Regarding the second Clinical guideline, early onset of neonatal infection, as cost reduction were considered: number of venepunctures for full blood count and C-reactive protein using the empirical therapy for all term newborns having prenatal maternal risks for infection, recommendation to cease the therapy following normal levels of white blood cells and neutrophils, etc.

Unfortunately, the exact cost-reduction can not be calculated due to the type of reduction (mainly qualitative reduction, meaning time consuming, health benefit for the baby etc). The credibility of pharmacoeconomics lies in developing studies in accordance with generally applicable standards of analysis and interpretation. Then users can translate pharmacoeconomic research findings into practices to ensure that decision makers allocate scarce health care resources wisely, fairly, and efficiently.⁴

Moving toward more evidence-based practice has the potential to improve quality and safety while simultaneously reducing costs, thus improving the outcomes of the Pharmacoeconomics. This field of the pharmacotherapy becomes increasingly important in terms of patient safety and national cost saving, thus enabling the relevant authorities to reallocate the resources.

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P10

DIRECT AND INDIRECT COSTS OF RHEUMATOID ARTHRITIS IN MACEDONIA

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Key words: Rheumatoid arthritis, direct medical costs and indirect cost

Introduction: Rheumatoid arthritis (RA) is an inflammatory form of arthritis that causes joint pain and damage with collateral effects on other organ systems. RA can progress steadily if untreated and can lead to impairment of physical function affecting basic activities of daily living such walking, eating, standing, and gripping. After 10 years, 50% of patients can continue to work or function normally on a day to day basis. It may also cause anemia, fatigue and shorten life expectancy. The prevalence of RA in Europe is 870 per 100 000 inhabitants. Country specific prevalence is varying at around 1%, as is in France (0.8%), Germany (1.1%), Italy (0.9%), Spain (0.7%) and UK (1.1%). The main goal in this analysis is to estimate the direct medical and indirect costs of RA treatment in Macedonia. Direct medical costs are the medical costs that result directly from the treatment of the disease.

Direct medical costs include:

1. Hospitalization costs
2. Ambulatory costs
3. Costs for treatment of articular manifestations of RA
4. Costs for treatment of extra-articular manifestacions of RA

Data for hospitalization costs has been taken from the register book for hospitalized patients at Rheumatology Clinic – Skopje, Macedonia (this clinic is the only specialized center for treating and hospitalizing patients with RA in Macedonia). All data for patients, hospitalized with RA at the Rheumatology Clinic, have been processed in order to determine the average cost for hospitalization per patient. This has been calculated by multiplying the average number of yearly hospitalizations per patient and the prevalence of DRG codes for their hospitalizations. According to DRG standards the average yearly cost for hospitalization at Rheumatology Clinic per patient is 29,101.00 MKD. The average ambulatory cost per patient has been taken from Informatics Center at Rheumatology Clinic. Average ambulatory cost per patient per year is 11,918.04 MKD. In order to calculate the costs for treating articular and extra-articular manifestations of RA prevalence, data has been taken from official publications. The average cost for treatment of articular manifestations of RA per patient is 293,363.83 MKD. The average cost of extra-articular manifestations of RA per patient is 66.453,12 MKD. The total direct

medical costs in patients with RA in Macedonia will be 400.697,44 MKD, this is shown on Table 1.

Table 1. Total direct medical costs

| Direct medical costs | Yearly costs per patient in MKD |
|---|---------------------------------|
| Hospitalization costs at Rheumatology Clinic | 29.101,27 |
| Ambulatory costs at Rheumatology Clinic | 11.918,03 |
| Costs for treatment of articular manifestations of RA | 293.363,83 |
| Costs for treatment of extra-articular manifestations of RA | 66.453,12 |
| Total direct medical cost | 400.697,44 |

Indirect costs involve the costs that result from the loss of productivity because of illness.

Indirect costs include:

1. Costs for invalid pension
2. Loss of productivity (GDP/No. of employed)
3. Loss of Health Insurance Aid (9.2% of average gross salary)
4. Family nursing costs

Data for indirect costs have been taken directly from Macedonian Government official web sites.

Total indirect costs per patients with RA is 836.217,32 MKD, these are shown on Table 2.

Table 2. Total indirect costs

| Indirect costs | Yearly costs per patient in MKD |
|------------------------------------|---------------------------------|
| Costs for invalid pension | 102.720,00 |
| Loss of productivity | 654.320,50 |
| Loss of Health Insurance Aid | 28.956,82 |
| Costs for homecare of other person | 50.220,00 |
| Total indirect costs | 836.217,32 |

Results and discussion: Based on this analysis we can calculate the total direct medical and indirect costs of RA in Macedonia per patient. Total direct medical and indirect costs of RA in Macedonia per patient is 1.236.914,76 MKD, these are shown on Table 3.

Table 3. Total direct medical and indirect costs of RA

| Direct and indirect costs | MKD |
|---|--------------|
| Direct medical costs | 400.697,44 |
| Indirect costs | 836.217,32 |
| Total direct medical costs and indirect | 1.236.914,76 |

Conclusion: This analysis estimates the RA costs per patients in Macedonia in terms of direct medical cost (Hospitalization costs, Ambulatory costs, Costs for treatment of articular manifestations of RA and Costs for treatment of extra-articular manifestations of RA) and indirect cost (Costs for invalid pension, Loss of productivity, Loss of Health Insurance Aid and Family nursing costs). According to this analysis total direct medical costs and indirect costs per patient is estimated to be 1.235.914,32 MKD showing that RA exerts a big economic impact from socioeconomic perspective.

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P11

CEPHALOSPORIN'S CONSUMPTION IN ALBANIA DURING 2011-2012

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Key words: Antibacterial consumption, drug utilization, cephalosporins, Albania

Introduction: Studies show that antibacterial consumption is associated with the development of antibacterial resistance. (1) There are little studies on antibacterial consumption and less on its resistance in Albania. An important step in this direction is measuring the antibacterial consumption/utilization. (2) We choose to make further studies on the cephalosporin's subclass consumption as it is an important and commonly used subclass in Europe. (3, 4) Data on the cephalosporin's class were collected for the year 2011 and 2012 from the National Center of Drug Control (NCDC) (5) and the ATC/DDD methodology was used in order to measure the drug consumption. (6) Data on antibacterial for systemic use were collected and then cephalosporin's class were selected from the national drug register to enter to pharmaceutical market in Albania (hospital and outpatient use). Cephalosporins's were divided by ATC code, specifically J01DB, J01DC, J01DD and J01DE and then DDD per each class were assigned referring to the ATC/DDD guidelines of WHO online index, version 2014. (7,8) The refereed population taken into study was from the latest report of CENSUS 2011. (9) The consumption was calculated as Defined Daily Dose (DDD) and DDD/1000inhabitant/day (DID). (10)

Results and discussion: The total consumption of cephalosporin's subclass was (3.51 DID) in 2011 and (3.18 DID) in 2012. The first generation of cephalosporin's (J01DB), specifically cefazolin and cefalexin was the mostly used from the J01D in 2011 (1.66 DID) and a slightly decrease was observed in 2012 (0.95 DID). The second generation of cephalosporin's (J01DC), mostly cefuroxime and cefaclor was higher in 2012 (1.50 DID), where in 2011 the consumption was 1.28 DID. The third generation of cephalosporin's consumption (J01DD) mostly cefriaxone and cefixime, increased during 2012 (0.73), where in 2011 it was 0.55 DID. In the Albanian pharmaceutical market, during 2011 the fourth generation of cephalosporin's (J01DE), specifically cefipime was present and it's consumption was (0.02 DID), whereas in 2012 it was out of the market.

Table 1. Cephalosporin's consumption during 2011 – 2012 expressed in DID.

| Antibacterial | ATC | DDDs per 1000 inhabitants per day | |
|---------------|-----|-----------------------------------|------|
| | | 2012 | 2011 |
| | | | |

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| | | | |
|-----------------------------------|-------|------|------|
| Cephalosporins | J01D | 3.18 | 3.51 |
| First-generation cephalosporin's | J01DB | 0.95 | 1.66 |
| Second-generation cephalosporin's | J01DC | 1.50 | 1.28 |
| Third-generation cephalosporin's | J01DD | 0.73 | 0.55 |
| Fourth-generation cephalosporin's | J01DE | | 0.02 |

The overall consumption of cephalosporin's in 2011 and 2012 in terms of DIDs results higher than the consumption of J01D in the ambulatory care reimbursed by the Healthcare Assurance Fund during the same period (11), which refers only to the covered population. Although the overall consumption include even the hospital consumption of antibiotics, the difference with is too big (more than 9.5 times than the reimbursed cephalosporin's consumption (0.375DID)). There is a doubt that the out of pocket consumption is out of protocol referred to previous survey (12), and also the antibacterial prescription may be inappropriate. The average consumption in Albania results (3.345 DID) higher than the median consumption of the ESAC-Net, which in the last report was 1.6 DIDs (0.04-7.6 DID) (3).

Conclusion: Further studies have to be made in order to investigate the low level of antibacterial reimbursement consumption in confront of the high level of overall J01D class of antibacterial consumption. Also, it would be suitable that health institution take this data in consideration in order to improve the regulation and strategies regarding the antibacterial prescription, dispense and utilization even of those paid out of pocket. As we are sure that the treatment protocols used to prescribe reimbursed antibacterials referee to the standards approved by Ministry of Health, we are not sure that the out of pocket antibacterial prescription is in coherence with the treatment protocols, as suggested by a little survey made in Tirana (12). In order to make further conclusions, the research group is currently analyzing the overall consumption of antibacterial class and the results will be finalized soon.

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P12

PENICILLIN'S CONSUMPTION IN ALBANIA DURING 2011-2012

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Key words: Penicillins consumption, drug utilization, Albania

Introduction: Antibacterial consumption, its misuse and resistance nowadays are global public health concerns, but until now there is little evidence on the antibacterial consumption or resistance in Albania. There is a lack of monitoring on the antibacterial dispense in out-patient sector, in hospital care, and also on respecting the treatment protocols in general. As overuse and misuse of antibiotics are main drivers for antibiotic resistance(1), this leads us to necessary investigation for antibacterial consumption/utilization data. We primarily choose to study the penicillin's (J01C) consumption as it was reported by ESAC-Net (2) as the mostly consumed in the community in Europe. Data were taken from the National Center of Drug Control (NCDC)(3) for all drugs registered in 2011 and 2012 entering the pharmaceutical market in the country, for hospital and outpatient use and also data from the reimbursement scheme from the Health Insurance Fund (HIF) (4). The population taken into study was the residential population of Albania referring to latest Census report of 2011.(5) Antibacterial drug class was selected and divided by ATC code and class. We referred to the guidelines(6) for ATC code and DDD assignment for each drug of the penicillin's subgroup. The consumption was calculated as Defined Daily Dose (DDD) and DDDs/1000inhabitants/day (DID).(7,8)

Results and discussion: The total consumption referring to national reports shows a total penicillin's (J01C) consumption of 10.70 DID in 2011 and 10.48 DID in 2012. Where the penicillin's with extended spectrum (J01CA) were consumed 6.05 DID in 2011 and 6.93 DID in 2012. J01Ca is followed by combinations of penicillin's, including β -lactamase inhibitor (J01CR) with 4.62 DID 2011 and 3.48 DID in 2012. Beta-lactamase resistant penicillin's (J01CF) consumption was 0.04 DID in 2011 and 0.06 DID in 2012. Beta-lactamase sensitive penicillin's (J01CE) was not present in Albanian drug market in 2011 and by 2012 its consumption resulted of 0.002 DID.

Table 1.

| Antibacterial | ATC | DIDs | |
|---------------|------|-------|-------|
| | | 2012 | 2011 |
| Penicilins | J01C | 10.48 | 10.70 |

| | | | |
|---|-------|------|------|
| Penicillin's with extended spectrum | J01CA | 6.93 | 6.05 |
| Beta-lactamase sensitive penicillins | J01CE | 0.00 | none |
| Beta-lactamase resistant penicillins | J01CF | 0.06 | 0.04 |
| Combinations of penicillin's, incl. β -lactamase inhib. | J01CR | 3.48 | 4.62 |

Overall consumption of penicillin's in 2011 and 2012 in terms of DIDs results higher than the consumption of penicillin's in the ambulatory use and reimbursed by the HIF during the same period (9), which refers only to the covered population. Although the overall consumption include the hospital consumption of antibiotics, the difference with HIF is too big (more than 6 times than the reimbursed penicillin's consumption (1.6 DID) to be explained only by this factor. So there may be two scenarios: First the uncovered population consume far more penicillin's in the ambulatory use than the covered population, and second may be that even the covered population consume penicillin's out of the reimbursement scheme. However the two scenarios, there is a doubt that the out of pocket use is inappropriate and treatment protocols are bypassed (10). The overall consumption in Albania compared with the ESAC-Net report (11) is approximately the same with the EU median consumption, 9.7 DIDs, where the consumption ranged from 3.9-16.5 DIDs in 2011.

Conclusion: Due to our results and discussions, further investigation is needed in order to determine the reasons which lead to the different values of reimbursed and not reimbursed antibacterial consumption in the country. Two main elements have to be investigated a- the level of reimbursed health services access; b- as we are sure that the treatment protocols used to prescribe reimbursed antibacterials referee to the standards approved by Ministry of Health, we are not sure that the out of pocket antibacterial prescription is in coherence with the treatment protocols, as suggested by a little survey made in Tirana (12). In order to make further conclusions, the research group is currently analyzing the overall consumption of antibacterial class and the results will be finalized soon.

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P13

**INFLUENCE OF NEW GUIDELINES ON ANTIBIOTIC PROPHYLAXIS AND
THERAPY TO REDUCE THE COST OF ANTIMICROBIALS IN THE DEPARTMENT
OF UROLOGY, UNIVERSITY HOSPITAL DUBRAVA**

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Introduction: In order to rationalize the application of perioperative antimicrobial prophylaxis and therapy, taking into account the ISKRA guidelines [1] and the guidelines of the European Society of Urology [2], own system of perioperative antimicrobial prophylaxis and therapy is introduced in the Department of Urology, University Hospital .

Objective: To investigate the possible influence of the new guidelines implementation on reducing expenditure on antimicrobials and present the results of a retrospective analysis of the perioperative antimicrobial prophylaxis and therapy use in the department with regard to the pharmacoeconomic analysis.

Materials and Methods: The medical records of 44 randomised patients treated in the period from January 1 to June 30 2012th and 44 randomised patients treated during the same period 2013th were included. The number and proportion of patients according to the mode of administration of antimicrobial prophylaxis and therapy, the average duration of the application as well as the average daily cost of antimicrobial drug per patient (calculated according to the List of reimbursement from the 2013th [3]) were retrospectively analyzed.

Results: Prior to the implementation of own guidelines all patients received parenteral antibiotics, according to the findings of urine culture or attitudes according to some of the clinical guidelines. During this period all patients received perioperative antimicrobial prophylaxis, but none of the patients received only a single dose of antibiotic prophylaxis nor antimicrobial prophylaxis orally. The average duration of antimicrobial therapy was 5.48 days with an average daily cost from 109.50 Kn per patient. In the same period 2013th 45,4 % patients were receiving parenteral antibiotics, 11,4 % patients had no perioperative antibiotic treatment, 9,1 % patients received one-time antibiotic and 34.1 % patients received antibiotics only orally. The antibiotic was administered according to the findings of urine culture or on newly implemented clinical guidelines. The average duration of therapy was 5,09 days with an average

daily cost from 39,17 Kn per patient, which represents a saving of 64 % compared to the same period of the 2012th.

Conclusion: The application of the new guidelines contributed to a more rational use of antibiotics with significant cost-savings.

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P14

ETHICAL CONSIDERATIONS OF PERSONALIZED MEDICINE

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Key words: personalized medicine, ethics, issues, protecting privacy

Introduction: A definition by European Alliance Personalized Medicine (EAPM) states that personalized medicine most frequently refers to a medical model using molecular profiling for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and stratified prevention. It may also involve imaging and other technologies. Further, it is stated by EAPM that in practice, rather than having a unique treatment for each individual person, patients are sub-divided into groups based on their “molecular make up”, i.e. using biomarkers. This definition does not mention any of genetic or genomic profiling, primarily referring to pharmacogenetic and pharmacogenomic technologies. If we take into account that adverse drug reactions (ADRs) rank as fourth leading cause of death in United States (Lazarou, J. et al., 1998) and that ADRs are significant cause of morbidity (World Health Organization - WHO, 2006) with the fact that many diseases have a genetic component with tests already available, the role of pharmacogenetic, pharmacogenomic and other genetic and genomic research is priceless. But, at the same time all advantages and benefits of personalized medicine rises new ethical considerations, especially questions on patient’s privacy, confidentiality, data protection as well as patient’s right on equity.

Results and discussion: Genetics is the study of heredity (WHO, 2002) and genomics is defined as the study of genes and their functions, and related techniques (WHO, 2002; WHA, 2004). Thus, pharmacogenetics refers to genetic differences/genetic variations in metabolic pathways which can affect individual responses to drugs while pharmacogenomics is more complex and it analyzes entire genome – the complete set of DNA within a single cell of an organism. Genome contains deeply personal information and with fact that basic principle in bioethics is the moral right to self-determination – principle of autonomy , there are many questions that need to be answered as: 1. protection and safeguarding of private information; 2. obtaining of informed consent and of which kind; 3. which are the priorities for testing – common diseases, rare diseases, hereditary diseases, carcinomas etc.; 4. ownership on individual’s genetic information; 5. sharing information for population benefit; 6. “right to know” and “right not to know” genetic information; 7. communicating genetic information to relatives; 8. decisions “to treat” and “not to treat” and its legal implications; 9. what are implications for the future of patient; 10. should

children be tested for adult-onset diseases; 11. how to manage the right on equitable access to medicines; 12. how and at what extent information should be given to the patient; 13. are we developing techniques and personalized medicine only for those who can pay for it ... and finally - is it ethical to do these tests when majority of world's population lack basic health care, common medications and insurance? WMA Declaration of Geneva (May 2006) states: "... The health of my patient will be my first consideration; I will respect the secrets that are confided in me, even after the patient has died;... Modern version of Hippocrates oath written by Louis Lasagna (1964) states:...I will respect the privacy of my patients, for their problems are not disclosed to me that the world may know..... The main dedication of physicians was always to provide the best possible care for their patients. The ethical argument supporting techniques used for personalized medicine at the beginning was the need to reduce the incidence of mortality and morbidity caused by ADRs with later improvement of efficacy and finally, with diagnosis of different diseases and tumor subtypes. Hidden are the concerns about possible racial and ethnic discrimination, stigmatization of particular subpopulations, employment discrimination, and of special concern – patient's different emotional reactions. There are substantial concerns about commercially available direct-to-consumer DNA tests (i.e. 23andMe, decode genetics, Pathway Genomics, Interleukin Genetics, DNA Direct and others) with prices ranging from \$ 2000 to \$ 149 - who and how will interpret these results, will they be misused? The ethical issues that arise with the use and reuse of personal data from any kind of genetic or genomic tests, especially when biobanks are in question, needs collaboration and communication between legal, ethics, scientific, patient's as well as industry organizations, based on mutual recognition and trust to break existing barriers for the benefit of mankind.

Conclusion: Already, there are numerous examples for benefit from different genetic and genomic research so that need for implementation of policies that will ensure ethically sounded testing used for personalized medicine and ethical drug development, is clear. Large-scale international trials and research collaboration are preferred for pharmacogenomics and related biomarker technologies can be introduced in patient care. Informed consent (IC) for genetic testing should not be the paravane but fair and transparent consent for both sides that sign it (patient and physician) with all options listed so that patient can make a free and voluntary choice. Informed consent should be obtained after full genetic counseling and high level of privacy protection. IC for drug metabolism genotyping may only require standard IC with information which test will be performed and for what reason, and does not need a full genetic counseling. As ethics nowadays requires flexibility and if GCP harmonization was possible between the continents, why ethical considerations of personalized medicine could not be?

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P15

**POTENTIALLY INAPPROPRIATE PRESCRIBING IDENTIFIED BY TWO
DIFFERENT TOOLS AND HEALTH OUTCOMES ASSESSMENT**

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Key words: potentially inappropriate prescribing, Beers criteria, STOPP-START, health outcomes

Introduction: Elderly patients are at increased risk of adverse clinical outcomes such as hospitalization, falls, disability and mortality, directly involving increased consumption of health and social resources, being responsible for 70% of the pharmaceutical expenditure. The use of inappropriate medications is a major contributor to the risk of adverse events, especially in polymedicated patients aged 65 years old or more. Therefore, optimization of prescribing for this group of patients has become a major public health problem worldwide; the implementation and evaluation of screening tools is still needed to optimize the appropriate use of medicines. There is growing interest in finding mechanisms to define the adequacy of pharmacological treatments and develop protocols for screening of potentially inappropriate prescriptions (PIP) in the past two decades. Two types of methods are being used - implicit and explicit. Among the most used, there are Beers criteria and STOPP-START. Beers criteria have dominated the international geriatric literature since they were first described in 1991. They have subsequently been modified to facilitate their use in people living in the community and were revised in 1997, 2003 and 2012. STOPP-START criteria were first created in Ireland and their clinical development has been undertaken by the Society of Geriatric Medicine of the European Union. These criteria, organized by physiological systems, list the most common treatment errors and omissions in prescribing and are easy to relate to active diagnostics and the list of drugs that appear in computerized medical records of patients. The objective of our study was to evaluate the association between potentially inappropriate prescribing and health outcomes (specifically mortality, number of hospitalizations, domiciliary visits and emergency care) in an older people population at hospital discharge using two different tools for PIP detection (Beers and STOPP-START). The study population was patients hospitalized in the University Specialty Hospital of San Cecilio, Granada, Spain during 2011-2012 and the average follow up period was 415 days.

Results and discussion: 624 patients were included in the study, 55% women, with a mean age of 77.7 years (+ / -6.86 years). The patients had a Charlson Index average of 3.22. The average number of drugs prescribed at discharge was 8.55, with 47.92% of patients receiving more than 8 prescription drugs. The most frequently prescribed drugs at hospital discharge were Proton Pump Inhibitors in 72% of patients, followed by loop diuretics (44%), aspirin (33%), and beta-blockers (30%). A high frequency of prescribing was also observed for NSAIDs, warfarin, thiazide diuretics, oral and inhaled corticosteroids. The drugs most frequently listed as inappropriate using Beers criteria were alpha blockers, NSAIDs, and calcium antagonists; using STOPP criteria, aspirin and NSAIDs predominated. Among the events detected during monitoring stands out the frequency of hospital readmissions within 30 days after discharge, which is higher for patients without PIP ($p = 0.053$) and an increase in the mean of domiciliary visits (43.7 versus 29.7) in patients with PIP, almost significantly.

Table 1. Effect of PIP on mortality after hospital discharge

| | cOR | CI | aOR | CI |
|-------------------------|------|-----------|------|-----------|
| Gender (ref. men) | 1.10 | 0.73-1.67 | 1.04 | 0.66-1.62 |
| Age (per year increase) | 1.04 | 1.01-1.07 | 1.04 | 1.00-1.07 |
| Charlson index | 1.42 | 1.24-1.63 | 1.42 | 1.23-1.64 |
| No. of drugs | 0.99 | 0.94-1.05 | 0.96 | 0.90-1.02 |
| Aspirin | 1.72 | 1.04-2.85 | 1.74 | 1.02-2.97 |

In Table 1, the effect of collected variables on mortality is analyzed. Association was found with age, representing 4% increase of the annual risk and with Charlson Index, with an increased mortality risk of 42% for each point increase. The possible effect of therapeutic drug groups classified as inappropriate by each set of criteria was assessed. We did not find any significant association for Beers criteria. Using STOPP-START criteria for PIP detection, a significant and independent increase in mortality was observed when aspirin was improperly prescribed, which was not verified when all aspirin prescriptions were analyzed.

Conclusion: Our results do not confirm the existence of a relationship between PIP measured by Beers or STOPP-START criteria and the use of health services in the medium term, although a significantly higher number of domiciliary visits is recorded. The inappropriate prescription of aspirin according to STOPP-START criteria behaved as an independent risk factor for mortality. If we accept, as noted repeatedly in literature that the prescription of potentially inappropriate

drugs is associated with increased healthcare costs and adverse events, and that this effect is preventable, it is truly essential to further identify and evaluate specific tools that can detect inappropriate prescribing. Acting on it might improve the safety of drug treatments, particularly among elderly patients with multiple pathologies.

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P16

THE COST OF PREMATURITY

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Key words: preterm birth, prematurity, vaginal pH

Introduction: Prematurity is still a major problem not only in the field of obstetrics and perinatal medicine but also for the society as a whole, not to mention the burdens for the concerned infants and their families.(1) The financial burden of preterm birth (PB) is exceptionally high. The cost of care of premature in Germany is around €730 million per year. When this amount is added to the cost of clinical management of mothers with threatened PB which amounted to about €360 million, the total cost is more than €1 billion. These calculations do not include the cost of long-term care of children and adults with disabilities due to prematurity. (2) The annual cost for care of premature in Sweden is estimated at around €65 million (3), and the USA including caring for the mother, infant, and long-term care, estimates range around \$26 billion. (4) From everything stated above, it is clear that prevention of PB is an important task for perinatologists. The association between infections and prematurity has been proved in many studies and much research has focused on finding infectious risk factors suitable for screening. If early diagnosed, infections can often be treated effectively. The most of the avoidable causes are to be found among patients with ascending genital infections, urinary tract infections and sometimes with systemic infection, even parodontitis, thus suggesting to have the main emphasis on prevention of infections, not neglecting other causes (e.g. psycho-social stress) if possible. In cases of other causes the possibility of intervention and successful therapy is clearly not so good. (5) The human vagina possesses a bio-system which under normal conditions provides a balance between physiologic lactobacilli and pathogenic flora, and so ensures a good protection against the spreading of pathogens, including their ascension to the uterine cavity. Lactobacilli are the main regulating factor of the vaginal milieu, keeping the pH value at the vaginal introitus under 4,5. A simple way of measuring the vaginal pH is to use indicator strips which are introduced into the area of the vaginal introitus before vaginal examination and compare the color of the indicator with the corresponding color chart. Disturbance of the vaginal milieu means threatened infection. It can be detected by pH-measurement at regular intervals, before bacterial vaginosis or infection develops (6). The main reason for the good results is not the early detection of existing infections, but the early detection

of precursors, namely disturbance of the milieu. The German “Self-care” program promoted by Erich Saling, in which vaginal pH was measured by pregnant women twice a week, from the first trimester, showed that participation of only 50% of pregnant women may significantly reduce prematurity, thus leading to significant annual save of expenses. (7)

Results and discussion: The study conducted at the University Clinic of Obstetrics and Gynecology, Skopje, included 120 pregnant women <37 gw, divided in two groups - the first group – with vaginal pH measurement from the first trimester of pregnancy, and the second group - with preterm labor. In cases of elevated vaginal pH we started therapy with *Lactobacillus* or lactic acid locally and in cases of positive cultures we suggested treatment according to antibiogram. The results showed significantly lower percent of PB among women controlled from the first trimester (11% vs. 86%). These 11% were all near term (34-36gw), opposite to 86% from the other group, of which 17,4% were between 32-34gw, and 26,7% were <32gw. The risk for PB was eight times higher among women with elevated vaginal pH. The results from the study are in accordance with the statement of Saling and Caillouette that the routine vaginal pH testing by every pregnant woman is simple, inexpensive (certainly relative to the cost of a damaged child), can lead to better informed sex habits and better vaginal health. “How much more simple and inexpensive does the solution need to be?” (7)

Conclusion: Regular vaginal pH measurement from the first trimester of pregnancy is almost an ideal method for a reliable, rapid ‘bed-side’ risk assessment. It is easy, clinically simple strategy to identify the patient at risk and may achieve reduction in the rate as well as the cost of prematurity. Efficient screening should start early, before 16 gw and should be applied often enough.

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P17

**PHARMACOECONOMICS OF THE SHORT- TERM
PROPHYLAXIS OF THE HAE ATTACKS**

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Key words: Hereditary angioedema, short- term prophylaxis, C1 inhibitor, attenuated androgens, price

Introduction: Hereditary angioedema (HAE) is a rare disease with autosomal dominante inheritance, characterized by deficiency or dysfunction of C1 inhibitor (C1-INH). Typical clinical presentation includes recurrent angioedema, without urticaria and pruritus, that primarily affects the skin or the mucosal tissues of the upper respiratory and gastrointestinal tracts. Swelling maybe self- limited, but laryngeal involvement can lead to airway obstruction and even death. The prevalence in general population is 1: 50 000. There are 3 types of HAE. Type I HAE is characterized by low plasma levels ofl C1-INH protein. Type II HAE is characterized by normal to elevated C1- INH protein, but function is low. Type III HAE occurs mainly in women with normal functional and quantitative levels of C1-INH. Treatment approach consists of acute attacks therapy and prophylactic therapy. Prophylactic therapy can be short- term and long- term. Shor- term prophylaxis is indicated in situations that are recognized as triggers for attack, such as dental, oral and general surgery. Attenuated androgens are currently the initial mode of prophylactic treatment. Therapy should be minimized, balancing disease severity with minimizing adverse effects. The drug most commonly used is danazol, but all attenuated androgens are useful in treatment. The nano-filtered C1-INH concentrate is also labeled for short- term prophylaxis. The other opitions are antifibrinolytics and plasma products.

Discussion: There are few medications recognized as short- term prophylaxis of HAE attacks, with different mechanism of action, different adverse effects and different contraindications. Assuming effectiveness and safety profile among approved short- term prophylaxis reasonable options would be attenuated androgens and C1- inhibitor. There are no head- to- head randomized clinical trials comparing these medications. On the other hand, no one of these medications provides 100 % protection of HAE attacks. The price of therapy is also very important factor in making decisions, and big differences are presented in the table 1.

Table 1.

| | | | |
|---------|-------------|-------------|---------------------|
| Danazol | 600 mg/ day | Approx. 5 € | 5 days before and 5 |
|---------|-------------|-------------|---------------------|

FIRST MACEDONIAN AND FOURTH ADRIATIC CONGRESS ON
PHARMACOECONOMICS AND OUTCOMES RESEARCH

| | | | |
|--|---------|----------------|---|
| | | | days after surgery |
| C1 inhibitor (Berinert)* | 1500 IU | Approx. 4730 € | preferably within the hour before the procedure |
| Nanofiltered C1 inhibitor (Cinryze) | 1000 IU | Approx. 2000 € | preferably within the hour before the procedure |

*off- label use

In making decision process which short-term prophylaxis medication to chose, it is important to know what kind of surgery (minor or major) will patient undergo, is she/he already taking a long- term prophylaxis and what medications approved for prophylaxis are currently available at the hospital pharmacy.

Conclusion: Decision making while prescribing short- term prophylaxis should be pointed on the patient benefit considering all the facts about patient, procedure that patient will undergo and of course his prior experience with similar situations and prophylaxis if that one has already been taken. On the other hand, the question is also the price of these medications. That fact largely influence their affordability. Besides that, if the medicine is expensive and not the standard therapy for numerous patients, should it be always available at the hospital pharmacy. Or, maybe we can simply prescribe cheap, effective medicine as attenuated androgen is, whenever there are no contraindications.

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P18

**MANAGING PROCUREMENT AND SUPPLIES OF DRUGS AND MEDICAL
DISPOSABLES WITH ABC ANALYSIS IN CLINICAL HOSPITAL STIP**

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Key words: ABC analysis, managing inventory, product value

Introduction: Pareto, an Italian economist of the eighteenth century argued that the wealth of a country is in the hands of a small part of the total population, about 20%, while the remaining 80 % belonged to 10-20 % of the wealth. During time this theory proved to be true and is also called Pareto rule and the curve is called Lawrence curve. In fact, analogous imbalance in the distribution of wealth, but primarily inversely proportional between number and wealth (value) also exists in pharmacy (drugs and medical supplies). According to the theory of Pareto, but by empirical data as well, it can be seen that about 80 % of the value of all products held in stock belongs to 20 % of the products, while the remaining 80 % contributed only 20 % of the total value of stocks. The existence of this imbalance requires implementation of specific controls for specific types of products that will be reviewed based on their relative importance. ABC analysis gives us a criterion for selection of products that allows us to control inventory by dividing all products in three groups A, B, C:

- A group or products that are few in number , but cost much and that is why are vital from an economic point of view ;
- Group B or products that are more numerous, but still important ;
- Group C or many and cheap products .

Obviously it is more important to focus attention on the fewer number of major products, controlling the others occasionally. To implement this approach, ABC analysis is performed in the warehouse of the pharmacy which gives the hierarchy of products according to their importance. The importance of a product depends on the contribution of that product in the value of inventories. This means that the importance can be calculated by multiplying the amount of product delivered to the business units and its value, i.e. the purchase price. If the pharmacy has a computer program for managing inventory, usually an option of displaying the products in tables is available, ranging from most important to least important. We can choose the percentage that is of our interest. For example if you choose 60 % the program will give us those products whose value (supplied units are multiplied with purchasing price) represents 60% of the value of all goods in stock. It is still good if the pharmacy does not have such a program, as it is the case with our pharmacy. In this case a manual work is done and it is sufficient to keep detailed records of what and how is being delivered. Afterwards the delivered quantities are

multiplied with the purchasing price in Excel and as a result we get the same table. It can be seen that usually about 15-20 % of the products constitute 80 % of the total value of stocks and the others 20 - 30 % represent 90 % of the total value.

Results and discussion: ABC analysis is consist of three groups: A, B and C where certain product belongs. In which group a product will be classified depends on our analysis and does not mean that if a product has been classified in one group, should stay there forever because drug prices are constantly changing and with new research and development new drugs are becoming more important and old ones become less important. 'Relevance' as already mentioned is other characteristic of the products. Relevance not relate to the economic aspect, but the practical importance of the drug to patients. To simplify things, all products in the table will be classified as having the same importance, which is normal (No). Clearly, if we know which are the products that belong to the first two groups (A and B), we can concentrate on fewer products and be sure that we control 90 % of the costs. It should be noted that this classification is purely financial and does not take account of the fact that some products, although negligible in economic terms and therefore classified as C, are vital to the pharmacy. So, the results of the ABC analysis automatically reject products from Group C as unimportant. From the ABC analysis of data we can conclude that the Clinical Hospital - Stip is no exception in terms of Pareto's law. To avoid the catastrophic consequences of staying without these inexpensive but critical products , the ABC analysis can be corrected by dividing the products in stock not only by price , but also by objective importance: vital (Vi) , important (Im) and normal (No). By combining this division with the one given with the ABC analysis, we get the 3 × 3 matrix as shown in Table 1.

| A | B | C | |
|-----|-----|-----|--|
| AVi | BVi | CVi | Vi = products vital to the pharmacy (no remaining stock is disastrously) |
| AIm | BIm | CIm | Im = important products (should be avoided to stay without supplies) |
| ANo | BNo | CNo | No= normal products (can tolerate temporary lack of inventory) |

This way ABC analysis is becoming even more important because it takes into account the importance of the product and allows you to 'observe' the products with low price. The lack of these products would cause more damage than the costs of storing large amounts of inventory.

Table 2. Presentation of ABC analysis in clinical pharmacy, Clinical Hospital Stip

| Group | Number of products | Value (denars) | Percentage |
|-------|--------------------|----------------|------------|
|-------|--------------------|----------------|------------|

| | | | |
|--------------|------------|-------------------|-------------|
| Group A | 97 (12%) | 61.220.000 | 80% |
| Group B | 94 (11%) | 7.250.000 | 9,5% |
| Group C | 627 (77%) | 7.880.000 | 10,5% |
| Total | 818 | 76.350.000 | 100% |
| | | | |

Table 2 presents a real example of a warehouse at the pharmacy. We can note that about 800 different products in 2012 at the Hospital pharmacy - Stip , total value 76.35 million denars, less than 100 items (Group A) worth 61,220,000.00 million denars (or 80 % of the total value) and approximately 20 % of all articles (Group B + group C) or 700 items, worth more than 90 % of the total value (about 15.130.000, 00 den).

Conclusion: Research shows that Pareto's law is confirmed in the warehouse of the Hospital pharmacy - Stip. Conclusion is that the greatest savings in the work of a hospital pharmacy (and every other one) can be achieved if we focus on products from Group A, because they are most expensive, but with normal importance.

P19

THE EFFECT OF INTERNATIONAL PRICE REFERENCING IN BULGARIA

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Key words: price legislation, reference prices, price revision

Introduction: Variety of measures are introduced to control the growth of prices focusing either on demand or supply side of the utilization. Within supply side measures fall the price regulation, price freezing, positive or negative medicines lists, external and internal price comparison etc. External price comparison is performed at international level by comparing the prices in a selected basket of countries. Current study analyses the results of IRP in Bulgaria after the increase of the number of countries included in the referent basket.

Materials and methods: It is a prospective observational comparative study of the changes in prices in a selected target oncology therapy during 2008 – 2013. On a yearly basis was collected officially published information about the prices of the selected medicines. In total 12 INN presented in 37 dosage forms were included in the price analysis. Those were the top leading by expenses INN, for target therapy, oncology products, which during the start of the observation were all patented products.

Results and discussion: On July 12, 2012 the National Assembly approves Supplement of the Drug Products in the Human Medicine Act which sets forth new substantial amendments related to the pricing. According to the planned amendments, the Commission for Pricing and Reimbursement is substituted by a new body, the number of countries included in the reference basket increased from 13 to 17 countries, the price revision at 6 months period was introduced, and the necessity of positive reimbursement decision in 5 from those 17 countries was also imposed. The reference countries are organized in main and supplementary baskets. The main basket includes Greece, Romania, Portugal, Spain, Italy, France, Denmark, Finland, Estonia, Lithuania, Slovakia, Slovenia. The supplementary basket (Belgium, Latvia, Czech Republic, Poland, Hungary) is used only in cases when a product is not available in the main basket. The new P&R body – The National Council for Pricing and Reimbursement of Medicinal Products was established on 01/05/2013. The Council is composed of well known experts in the area with clear vision, who immediately started working based on the new rules. In the field of targeted therapy the prices were decreased on average by 19% - Table 1.

Table 1. Average price decrease by INN

| INN | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 |
|--------------|--------|--------|-------|--------|-------|--------|
| Capecitabine | -2.9% | -7.0% | -4.1% | -13.0% | -1.1% | -28.1% |
| Dasatinib | -3.0% | -2.3% | -1.4% | -0.2% | 0.9% | -1.8% |
| Erlotinib | -11.0% | -0.2% | -5.7% | -5.6% | -4.9% | -2.3% |
| Everolimus | | -1.0% | 0.4% | -2.5% | -6.7% | -3.6% |
| Imatinib | -5.6% | 0.2% | -0.1% | -2.8% | -2.9% | -1.6% |
| Lapatinib | | | -0.6% | -4.5% | -2.5% | -0.9% |
| Nilotinib | | | -3.4% | -17.0% | 11.6% | -3.1% |
| Pozopanib | | | | -2.9% | -3.9% | -0.3% |
| Sevelamer | -12.5% | -15.2% | 1.8% | -2.7% | -5.9% | -0.3% |
| Sorafenib | -5.2% | 0.8% | 0.6% | -4.0% | -2.5% | -2.4% |
| Sunitinib | -3.5% | -1.0% | -4.9% | -10.4% | 9.9% | -0.3% |
| Topotecan | | | -4.3% | -2.6% | -3.6% | -1.9% |

The consecutive yearly decrease is shown on the Figure 1 – 3. It is evident that the decrease is higher for the high prices INN and indications.

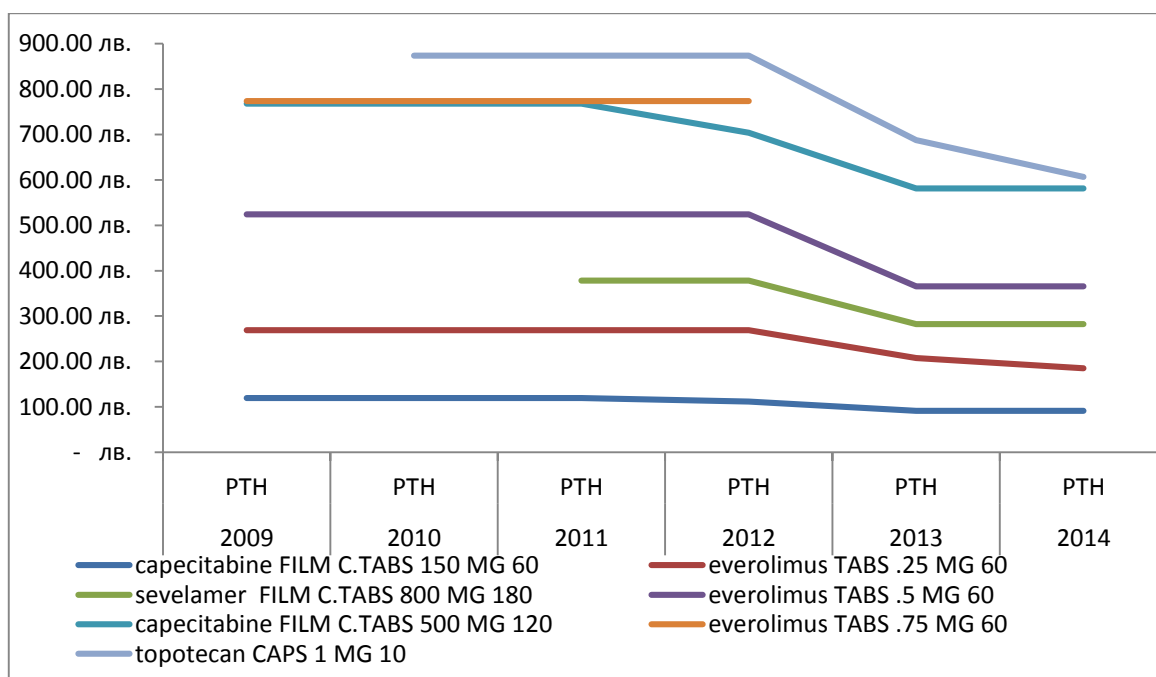


Figure 1. Price decrease in the group of low priced INN

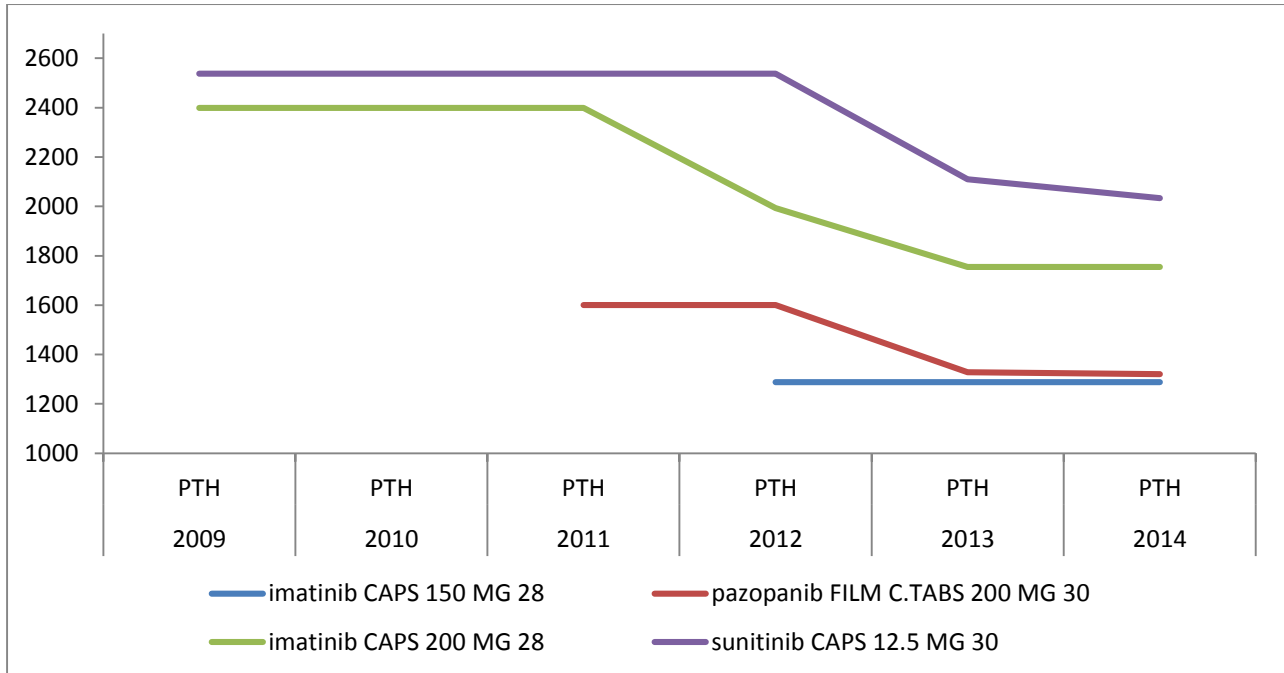


Figure 2. Price decrease in the group of medium priced INN

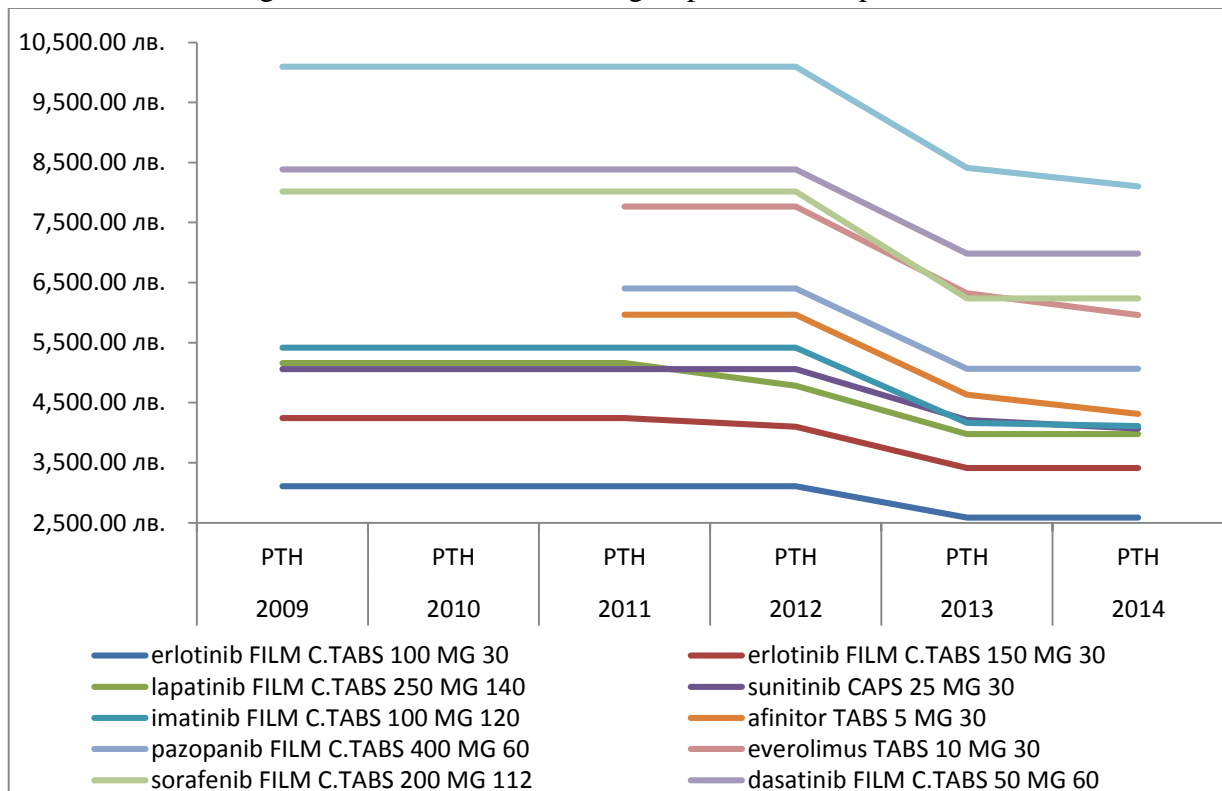


Figure 3. Price decrease in the group of high priced INN

For some of the INN an essentially similar alternatives were authorised during the observed period that also contribute to the overall positive process.

Conclusion: In general the increase in the reference basket countries, frequent price revision and creation of the National Council for Pricing and Reimbursement let to the significant decrease in the prices of target oncology therapy and create savings for the National health insurance fund for proximately than 5mln BGN in 2013.

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P20

**EVALUATION OF COST-EFFECTIVENESS OF COCLEAR IMPLANT USE IN
ALBANIA**

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Background: It is estimated that each year in Albania, about 70 children born with profound hearing loss. If detected and diagnosed early (before age 4-5 years) and treated with cochlear implant, these children are likely to recover the loss of hearing in a certain extent and to develop gradually the speech being integrated in life and society. If detected later or left untreated after the age of 5 years old, they lost the opportunity to fully develop their speech and so to communicate normally through language.

The purpose of this study is to compare these two alternatives by combining the costs and respective benefits or outcomes through a pharmacoeconomic evaluation. This assessment provides theoretical data on the problem of profound hearing loss mainly at children, long-term consequences of this condition in their life mainly in developing linguistic, cognitive (cognitive), emotional, and social benefits and highlights the impact of cochlear implant in the lives of these individuals.

Methodology: As for those individuals, their quality of life is compromised by their defect, we used a cost-utility analysis. The assessment is done from the perspective of the payer and the society. Because in our country there are no studies assessing the quality of life of children with profound hearing loss and the number of people (mostly children) who have undergone a cochlear implant to overcome their disability is small (< 15 individuals), it is impossible to extract significant result on benefits (utilities) that implant brought into their quality of life. In this case, we had extrapolated the utilities from reliable studies on literature. The study by Barton and colleagues in UK is considered to have given relevant assessing on the weight of the utility of children with profound hearing loss before and after cochlear implant. From this study the utility is estimated at 0.421 HUI (Health-Utility Index) for the first alternative (before implant) and 0.653 for the second alternative (after implant), with an addition of 0.232 in the HUI. Assuming that the cochlear implant or the state of profound hearing loss do not affect the life years of these individuals, for further evaluations will we took the average life expectancy in Albania that of 72 years (reported officialy). After assessment of costs and calculation of QALYs for each alternative we concluded.

Conclusions: Cochlear implant improves hearing perception and help the development of speech at young children with profound hearing loss under the age of 4-5 years. The benefits are as better as younger is the child. Cochlear implant improves the quality of life, outcomes in

terms of academic education and integration into society. Cochlear implant is more cost-effective from both perspectives considered by our the study (Payer and Society) compared with no implant. According to payer (State) perspective, by the application of alternative II (cochlear implant), there will be saved 73,243 euros over the life of an individual with profound hearing loss. According to the society perspective, by the application of alternative II (cochlear implant), there will be saved 287,443 euros over the life of the individual with profound hearing loss.

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**REFERENCE PRICING SYSTEM IN THE REPUBLIC OF MACEDONIA AND THE EU
COUNTRIES**

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Key words: Reference pricing system, reference price, reimbursement, drug pricing

Introduction: The reference pricing system in the Republic of Macedonia was implemented in 2008. In some European countries this system of regulation of medication prices dates back to late eighties and early nineties. This system, more than just a mere form of medication price regulation, is a governmental policy of these countries in order to reduce the expenses on reimbursed medications. This system enables involved parties to determine an acceptable price level for “equivalent” medications with huge difference in price (set by the producers). The reference price of a medical product implies the maximal amount, which is reimbursed by the Healthcare Insurance Fund. If the price of a medical product is higher than the reference price, then the patient pays only the difference between the price of a medical and the reference price or h/she gets a comparable therapeutic product (without additional charges). By limiting the prices for the producers as well as motivating the prescription of generic medications through the above-mentioned system, the level of expenses for reimbursed medications is reduced, whereas the patients are offered cheaper medication prices. Despite the debates and polemics on the consequences of this system, the RPS is currently applied in the majority of EU countries. This article will focus on the differences that exist in the organization of the RPS in some EU member countries and we will also analyze the “Methodology of formulating the prices of medications” in Macedonia and the consequences that derive from this system.

Results and discussion: The Reference Pricing System is a system of controlling and stabilizing the prices of reimbursed medications. In Europe, this system was adopted in countries with high medication prices and then widely spread in many other European countries. The table below shows countries that have implemented the RPS and those which have not done so yet.

Table 1. Some European countries that have implemented the RPS

| Imp. Year | Countries with RPS | Countries without RPS |
|-----------|----------------------------------|-----------------------|
| | Austria, Norway, Sweden | |
| 1989 | Germany | |
| 1991 | Netherland | |
| 1993 | Denmark | |
| 2000 | Spain | |
| 2003 | France, Portugal, Italy, Hungary | |

The difference in defining *drug classes* – is one of the most frequently discussed matter. The criterion for the group of medications that are considered as “interchangeable” varies from one country to another.

Three types of medication classification have been identified:

- ✓ Type I – grouping of bio-equivalent medications (ATC-5)
- ✓ Type II - grouping of chemically different but pharmacologically identical medications (ATC-4)
- ✓ Type III - grouping of pharmacologically different but therapeutically identical medications (ATC-3)

Table 2. Medication grouping in different countries

| County | RPS Level | ATC |
|-------------|------------------|---------------------|
| Belgium | Level I | ATC 5 |
| Germany | Level I, II, III | ATC 5, ATC 4, ATC 3 |
| Netherlands | Level II | ATC 4 |
| Hungary | Level I, II | ATC 5, ATC 4 |
| Italy | Level I, II, III | ATC 4, ATC 3 |
| Spain | Level I | ATC 5 |
| France | Level I | ATC 5 |
| Denmark | Level I | ATC 5 |
| Portugal | Level I | ATC 5 |
| Bulgaria | Level I, II | ATC 5, ATC 4 |
| Slovenia | Level I | ATC 5 |

Different methods of calculating the referent price

- Based on the lowest priced medications: Denmark, Italy, Poland, Slovenia, France, Hungary, Turkey
- Based on the percentage of original drug: Belgium
- Based on the econometric model: Germany
- Based on the average price of medications: Croatia, Hungary

Referent Pricing System in Macedonia

RPS was implemented in Macedonia in 2008. The Macedonian government adopted the book of rules on “The methodology of establishing medication prices”. Based on this methodology, the wholesale and retail prices of medications are established in accordance with medication prices in referent countries, such as UK, Serbia, Slovenia, Bulgaria, France, Croatia, Germany, Turkey, Russia and Greece.

Conclusion: RPS has been adopted as a mechanism by governments to reduce the cost of expenses in the public healthcare system. By setting a limit price, competition among producers is fostered. The establishment of a reference value also makes the patients more aware of the medication prices. The determination of prices by using this system influences the compilation of positive lists whose main objective should be cost-saving. However, even though this system has been implemented in almost all European countries, there are still no sufficient analyses of the achieved results and outcomes.

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P22

**NEW GUIDELINES IN PHYSICAL THERAPY – HOW TO RATIONALIZE AND
IMPROVE EFFICIENCY**

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Key words: physical therapy, business processes, improved efficiency

Introduction: Current guidelines and business processes in physical therapy in Croatia are not aligned with EU guidelines and practices. As it is now, it is possible to incur significant unwanted costs due to very high unrestrictive number of procedures included for only one referral. Due to strict division of business processes and roles between doctors and physical therapists, which did not change for decades, many unnecessary examinations are performed. Moreover, there is a great opportunity for increasing the managing role of physical therapists to release the burden of doctors and provide better care.

Results and discussion: EU and especially Slovenian practice demonstrates that giving more active role to physical therapists gives much better clinical results and saves significant costs. According to WCPT¹, physical therapists should be also the first contact, able to assess and treat patients/clients without referral from a medical practitioner or other third party. In this study we have tried to estimate clinical, practical and economic benefits of this new model of physical therapy in Croatia.

Conclusion: Besides the adapted clinical guideline, new model for physical therapy tariffs based on time frame and not only procedures should bring significant savings and release resources for closing budgets in physical therapy. Releasing the burden from doctors, and giving more patient management roles to physical therapists leads to optimization and rationalization of costs. New tariff and costing schemes enable better control over the process and budgets in physical therapy.

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P23

**POSSIBLE BENEFITS OF CYP2D6*4 PHARMACOGENETIC TESTING IN BREAST
CANCER PATIENTS FROM KOSOVO**

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Background: Breast cancer is a costly illness which is responsible for 14% of cancer deaths among women. The financial costs of cancer are high for both the person with cancer and for society as a whole. Treatment options for this disease include radiation, lumpectomy, mastectomy, chemotherapy, or a combination of these options. Chemotherapy for breast cancer includes traditional chemotherapy, hormonal therapy, and targeted therapy. Tamoxifen is a widely prescribed hormonal therapy drug for the treatment of all stages of estrogen receptor (ER)-positive breast cancer and is also widely used for breast cancer prevention in high-risk women. The cytochrome P450 2D6 (CYP2D6) genotype is one of the determinants of the plasma concentration of 4-hydroxy-N-desmethyltamoxifen (endoxifen), an active metabolite generated from tamoxifen with CYP2D6, and is one of the strongest predictors of tamoxifen response in breast cancer patients. Variants in the *CYP2D6* gene can cause patients to be either intermediate or poor metabolizers, thereby rendering tamoxifen treatment less effective. The *CYP2D6* gene has multiple allelic variants, some of which, including the *4 allele, result in the loss of CYP2D6 enzyme function.

Objectives: The objective of our study was to determinate whether or not testing for cytochrome P450 2D6 (CYP2D6) polymorphisms in women with early hormone receptor positive breast cancer leads to improvement in outcomes, is useful for health decision-making and is a cost-effective use of health-care resources.

Methods: A total of 110 patients with breast cancer from Kosovo, who had been taking 20 mg/day of tamoxifen (TAM patients) for at least 4 weeks as adjuvant therapy (patients who were co-prescribed CYP inhibitors were excluded) were included in this study. Genomic DNA was extracted from whole blood, using a QIAGEN DNA extraction kit and the procedure recommended by the manufacturer (QIAGEN AS, Oslo, Norway). The presence of the CYP2D6*4 polymorphism *CYP2D6*4* (1846G > A; rs3892097), was analyzed by the allelic discrimination TaqMan assay (MxPro 3005P, Strategene, La Jolla, CA) according to the manufacturer's instructions (Applied Biosystems, Foster City, CA). The study was approved by Ethics Committee of University Clinical Center of Pristina. A review of economic evaluations and models of CYP2D6 testing for patients treated with TAM was carried out. Official data

about annual number of patients with BC, cost for treatment and utilization of Tamoxifen were obtained from official institutions in Kosovo. Cost of pharmacogenetic CYP2D6 testing was calculated according to the standard protocol for this analyses and the price of reagents, laboratory equipment and human resources in Center for Biomolecular Pharmaceutical Analyses (CBPA), Faculty of Pharmacy, Ss Cyril and Methodius – Skopje, R.Macedonia.

Results: According to the official data from Oncology Institute in Kosovo, there were 250 new breast cancer cases in 2013 in Kosovo. The consumption of Tamoxifen tablets procured by MoH through tenders in 2011 was 30720 tablets with unit price 0,07 eur per tablet, 33160 tablets in 2012 with unit price of 0.097 eur per tablet and 32000 tablets in 2013 with unit price of 0.097 eur per 20mg tablet. The total amount that Republic of Kosovo spent as a direct cost for Tamoxifen therapy in 2013 was 3104 euros. The genotypic frequencies of the CYP2D6*4 polymorphism in all patients were GG (63,8%) GA(28,9%), and AA(7,3%). The distribution of all genotype frequencies did not deviate significantly from Hardy–Weinberg expectations. The CYP2D6 mutant allele in breast cancer patient from Kosovo has similar distribution (7,33%) as determined in other European populations. In our study the TAM patients homozygous for the CYP2D6*4 allele have a higher risk of disease recurrence (3 out of 8 patients with AA genotype and 9 out of 67 patients with GG genotype) and they were associated with the occurrence of breast cancer in the early age (39 years for patients with AA genotype in comparison with 50,6 years in GG patients for CYP2D6*4). The total cost for pharmacogenetic CYP2D6 testing in Center for Biomolecular Pharmaceutical Analyses (CBPA), Faculty of Pharmacy, Ss Cyril and Methodius – Skopje, R.Macedonia is 35eur per patient. We still have controversial cost-effective information about pharmacogenetic CYP2D6 testing in patients with breast cancer who are on Tamoxifen therapy, but should be viewed as an investment in individualized patient therapy for the prevention of life-threatening recurrences.

Conclusion: The CYP2D6*4 polymorphism plays an important role in breast cancer etiology as well as in determining the hormonal therapy where tamoxifen is used. CYP2D6 genotype testing led to changes in therapy among poor metabolizers, even in the absence of definitive data that an alternative medicine improved outcomes. More clinical research is needed before we can recommend routine CYP2D6*4 testing and we can rationally use this test in to daily practice. Physicians should be prepared to share with patients information about availability and clinical-effectiveness of this testing.

P24

**COST AND SAFETY ANALYSIS OF LOW MOLECULAR WEIGHT HEPARINE
USAGE DURING PREGNANCY**

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Key words: pregnancy, hyper thrombotic condition, low molecular weight heparine

Introduction: Thromboembolism is the main cause of maternal mortality in developed countries. Venous thromboembolism (VTE) remains one of the most important cause of death during pregnancy. The risk is increased in women older than 35 years, those with previous VTE, operative delivery and underlying thrombophilia. Recent studies have indicated that certain low molecular weight heparine (LMWH) given subcutaneously may replace continuous intravenous unfractionated heparine for the treatment of venous thromboembolism. LMWH have a predictably high absorption rate when given subcutaneously and they do not require laboratory monitoring. These characteristics of LMWH raise the possibility of treating uncomplicated patients with deep venous thrombosis in the outpatient setting. Our study represents a retrospective study that was conducted at Clinical Hospital in Tetovo, Department of Gynecology and Obstetrics. The study was undertaken during January 1st – December 31st 2012. During that year, it was noticed an increase of LMWH usage for the diagnosis hyper thrombotic condition. The objective of this study, based on these dates, is to show the cost differences between inpatient and outpatient treatment.

Results and discussion: During the period January 1st – December 31st 2012, were registered 4636 patients. 2324 (50,19%) of them delivered, 534 (11,52%) were patients with other diagnosis, 331 (7,14%) had miscarriage. 1447 (31,21%) of them were pregnant women, from that number, to 298 (20,59%) of them was prescribed LMWH.

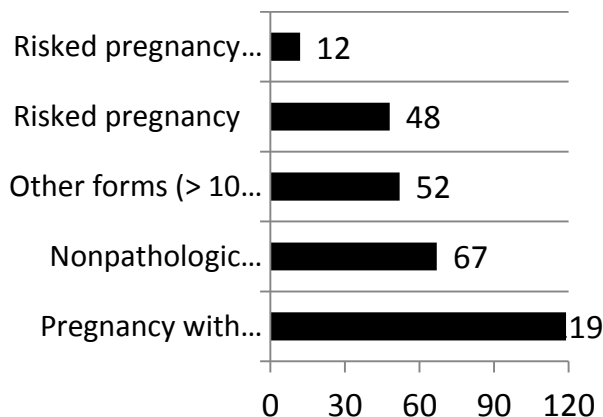


Figure 1. Types of diagnosis among pregnant women

From 298 pregnant women who appeared as outpatients, to 119 (39.93%) of them transfusiologist proscribed a therapy for the diagnosis hyper thrombotic condition. 67 (22.48%) had nonpatological pregnancy, but high levels of Dimers, 48 (16.11%) of them were with risked pregnancy and 12 (4.03%) of them had risked pregnancy associated with hyper thrombotic condition. The other 52 (17.45%) were with different diagnoses: pregnancy after IVF, pregnancy associated with diabetes, pregnancy after miscarriage and other.

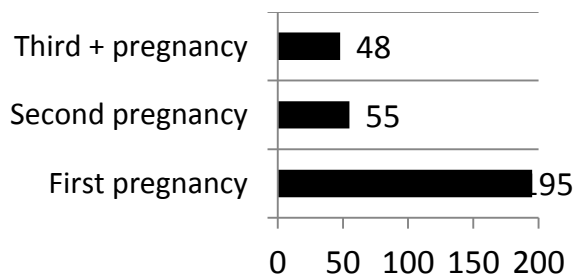


Figure 2. Ordinal number of pregnancy

For 195 (65.44%) women, this was their first pregnancy, 55 (18.46%) declared that this is their second pregnancy, and for 48 (16.10%) women, this was third, fourth or fifth pregnancy (3+). At the department of Gynecology and obstetrics, there are used five types of anticoagulants recommended by the transfusiologist. The most used anticoagulant was Clexane 2000 unites – 2188 ampules (38,12%), the detailed explanation is given into the Table 1. HFIM pays to the hospital an amount of 130,00 MKD for each ampule application, it also pays 390,00 MKD for the entire period of hospitalization.

Table 1. Anticoagulants, number of ampules and the total cost

| Anticoagulants | Ampules | | Total cost of ampules (MKD) |
|----------------|---------|---|-----------------------------------|
| | No. | % | |
| <hr/> | | | |

| | | | |
|---|-------|-------|------------|
| Clexane 2000 | 2.118 | 38,12 | 262.608,00 |
| Clexane 4000 | 1.021 | 17,79 | 211.632,00 |
| Fraxiparine 0.2 | 32 | 0,56 | 3.584,00 |
| Fraxiparine 0.3 | 1.402 | 24,43 | 156.082,00 |
| Fraxiparine 0.4 | 1.097 | 19,11 | 170.539,00 |
| Total Cost | | | |
| (Ampules + Application + Hospitalization) = | | | |
| 1.354.948,00 MKD | | | |

Conclusion: The change in the manner of prescribing different types of LMWH, will result with large cost savings for the healthcare system with no apparent changes in effectiveness. In that case, HFIM will not have to pay 390 MKD for hospitalization and 130 MKD for each given ampule.

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P25

**USE OF ANTIBIOTICS IN PUBLIC HOSPITAL INSTITUTE OF NEPHROLOGY –
STRUGA IN THE PERIOD 2007 – 2012**

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ABSTRACT

Background: Use of parenteral antibiotic therapy is investigated in the ambulatory patients, hospitalized ones and patients on ambulatory hemodialysis at the PHI Institute of Nephrology – Struga within the period of 2007 – 2012.

Objective: The aim of our work is an assessment of the use of antibiotics depending on the patient's needs.

Materials: The data analysis of use of antibiotics by hospital's departments at PHI Institute of Nephrology – Struga for period of five years.

Results: Hospital's budget spent for antibiotics in 2007 was 395.689 denars (6.434 EURO); in 2008 - 504.762 denars (8.207 EURO); in 2009 – 1.305.350 denars (21.193 EURO); in 2010 – 1.142.060 denars (18.570 EURO); in 2011 – 587.382 denars (9.550 EURO); and in 2012 - 981.435 denars (15.958 EURO).

Conclusion: Highest amount of the hospital budget has been spent for cephalosporins, the most used antibiotic as well.

P26

**CASE STUDY OF TRANSPLANTATION AND IMMUNOSUPPRESSANT THERAPY
IN MACEDONIA – FIVE YEAR FOLLOW UP 2009 – 2013**

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Key words: Immunosuppressive, organ transplantation, budget, health insurance fund, five year follow up, Macedonia

Introduction: Aim of the study is to follow up the last years presented situation with organ transplantation and immunosuppressant therapy in Macedonia. Immunosuppressant therapy is essential for patients after transplantation, in order to suppress immune response, to prevent rejection of grafts or transplants. Organ transplantation has increased in last five years, with last years cadaveric transplantation, as last stage of transplantation protocol project. Kidney, liver and bone marrow are tree organs that are actively transplanted in Macedonia. In 17 years, more than 200 patients received kidney, mostly from live organ donor, till 2013 when first cadaveric organ transplantation was conducted. All transplanted patients started initially with immunosuppressive therapy, and take lifelong doses. Bone marrow transplantation is active for 14 years and total 270 patients are transplanted, annually approximately 20 – 25. One third of all are allogenic (other donor) transplantations, which by the protocol get immunosuppressant therapies, mostly cyclosporine and mycophenolate mofetil, at least for the first six months. Liver transplantation started 2011 one child is transplanted and started with tacrolimus. Twelve immunosuppressant products are registered in Macedonia of which two cyclosporine, two antithymocyte immunoglobulin, four mycophenolate mofetil, tacrolimus, daclizumab, basiliximab and everolimus, of which six are not marketed at all. Five generics are on reimbursement list of HIF, but only three of them are marketed. Data for spending for immunosuppressant's are obtained from Health Insurance Fund (HIF).

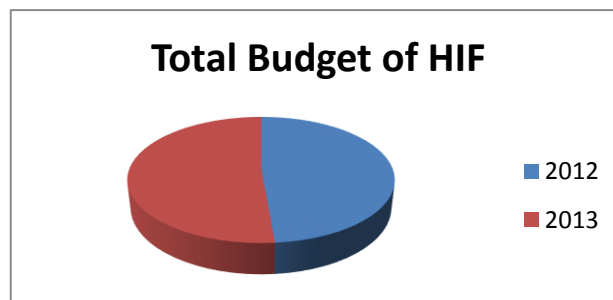
Results and discussion: Results for cost for immunosuppressive therapy for last five years are shown in table 1, according to the Health insurance fund annual reports for the last five years. In table is shown percentages from total budget of HIF in Macedonia that are spend for immunosuppressive therapy, but also you could see variety (VAR%) in percentages of spending for immunosuppressive, from total budget.

Table 1. Five year analysis of HIF spending for immunosuppressive therapy

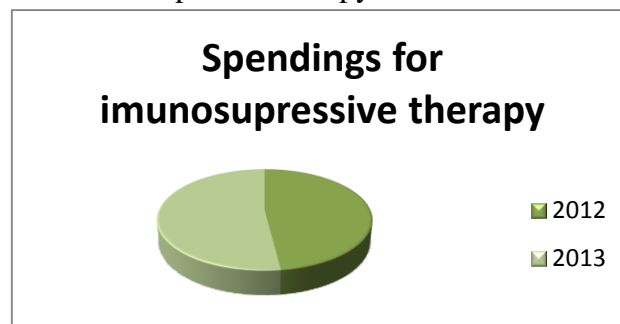
| Year | Cost for immunosuppressive therapy (Eur) | Percentage of total budget of HIF (%) | VAR % of total budget versus previous year |
|------|--|---------------------------------------|--|
| 2009 | 593.000 | 1.15 | - |
| 2010 | 522.000 | 0.86 | - 26 % |
| 2011 | 590.000 | 0.99 | 15 % |
| 2012 | 472.000 | 1.45 | 46 % |
| 2013 | 511.000 | 1.49 | 3 % |

Although total budget of health insurance fund increased from 2012 to 2013 for 5.5%, increase of spending for immunosuppressive therapy in 2013 increased for 8% according to 2012.

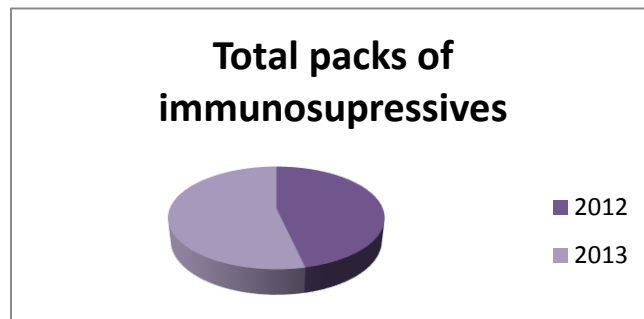
Picture 1. Total budget for medicines of Health insurance Fund in Macedonia 2012 vs 2013



Picture 2. Spendings for immunosuppressive therapy from Health insurance Fund 2012 vs 2013



Picture 3. Variation of packs of immunosuppressive therapy 2012 vs 2013



Variation of packs of immunosuppressive therapy showed that 15% more immunosuppressive were spend in 2013 vs 2012, nevertheless that total budget spend was only 8% more in 2013 vs 2012. This showed that continuous price reduction of medicines in last few years in Macedonia, resulted in more pack spend for fewer budgets from Health Insurance Fund. Positive transplantation campaigns in all fields in Macedonian Health care system was followed by spending for immunosuppressive therapy.

Conclusion: In Macedonia there is trend in continuous price reduction of the medicines, at least twice a year. New investments and opportunities for transplantation of organs bring more transplanted patients annually, but less spending from HIF for immunosuppressive therapy.

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P27

CUTTING COSTS IN HYPERPHOSPHATEMIA – A COST MINIMIZATION STUDY

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Key words: hyperphosphatemia, calcium acetate/magnesium subcarbonate, cost minimization, phosphate binders.

Introduction: Hyperphosphatemia is a very serious condition which impacts increased mortality risk in patients who are undergoing chronic dialysis. Due to related secondary decrease of serum calcium as well as reactive elevation of parathyroid hormone, there is high risk of renal osteodystrophy. Furthermore, uremic arteriopathy and cardiovascular calcification are developed which increases cardiac conditions in terminal renal failure. Therapy for hyperphosphatemia is performed with nutritional restrictions and dialysis, as well as with phosphate binders based. A cost minimization analysis was performed to assess costs and outcomes for calcium based binders and calcium and magnesium based binders (calcium acetate/magnesium subcarbonate, calcium carbonate and sevelamer).

Results and discussion: In phosphate binders selection is determined by price. Calcium acetate/magnesium subcarbonate has comparable efficacy toward other non calcium phosphate binders and superior to calcium phosphate binders. Superiority toward calcium based phosphate binders lays in lower risk of hypercalcaemia, potential delay of calcification due to magnesium and in regulation of parathyroid hormone. Recent Cochrane analysis¹ demonstrated that agents based on calcium should be used in first line, since they are cheaper better tolerated and of equal efficacy as sevelamers and lanthan carbonate.

Conclusion: No difference in strength, side effects, morbidity or mortality among phosphate binders exist, however difference in costs is present and significant. This analysis has demonstrated that calcium acetate/magnesium subcarbonate is dominant bringing high savings to health insurance due to its low cost and comparable efficacy.

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P28

REIMBURSING HEARING DEVICE FOR CHILDREN - WHY DOES IT MATTER

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Key words: hearing aids, children, pedacoustics, reimbursing.

Introduction: Allocating hearing aids in children population depends on various factors: age, degree and type of hearing impairment, social environment and child and family behavior. In Croatia, mandatory screening for newborns enables identifying children with potential hearing impairment and through monitoring these children may have prevented more severe hearing disorders. Features of hearing devices for children differ significantly than for adults. Currently no hearing aid adapted for children is reimbursed by Croatian health insurance. We have used a budget impact model to estimate the impact of reimbursing a new device specifically manufactured for children, and assessed outcomes and costs related to included diagnostics and adaptation in our model.

Results and discussion: New hearing devices manufactured for children are adapted for anatomy of child`s ear, prevent microphonia, have protected and tamperproof and waterproof case, have extended frequency range and have premanufactured and adapted input audio levels. These and other characteristics prevent from device damage, unintentional changing of hearing levels, allergies and hearing damaging. Such devices also bring higher patient (child) compliance and bring better results in language and hearing acquisition. Also, diagnostics and adaptation for the hearing device make huge part of future success with the device.

Conclusion: Reimbursing hearing aids brings savings in a model with longer time frame than proposed three years. Prevention of serious hearing damages in later age due to late allocation of hearing device or inappropriate device for children is evident in at least ten year horizon. In a context of budget impact climate, due to tightened health care budgets, alternative models should be considered such as cost effectiveness models.

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P29

**AN OVERVIEW OF THE IMPACT OF RECENT ECONOMIC RECESSION ON USE
OF MEDICINES**

Verica Ivanovska

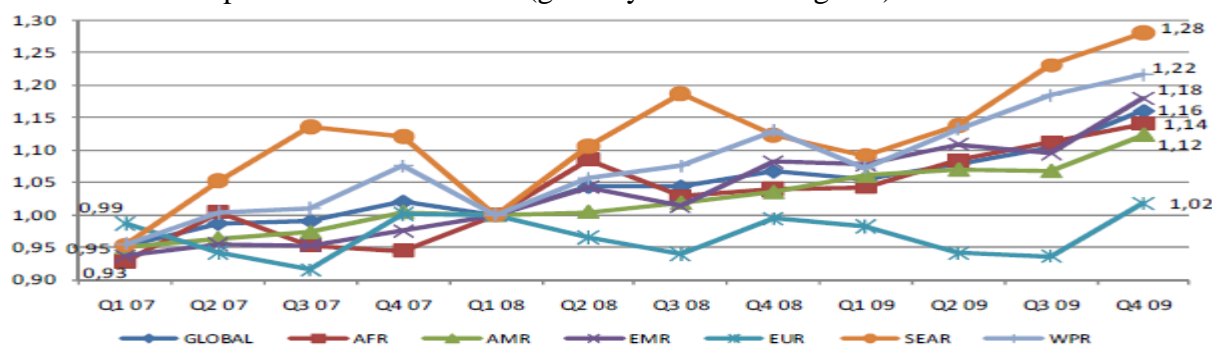
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Key words: economic recession, use of medicines, medicines prices

Introduction: Most of health care spending in Europe is financed by public budgets. However, the increased health care demands, aging population and global economic recession trends can impair the access to health services and control of health care expenditure. Historically, the recession has had negative impact on public health as a result of a strong correlation between the weak economic situation, decreased utilization of health care services and worsened health indicators. In such circumstances, health care (including pharmaceutical) costs, are rationalized both at patient and public sector level. The measures to control public drug spending may include regulations on medicines prescribing and use and pharmaceutical pricing policies. Financial regulatory measures include the methodology of reference drug pricing, competitive tenders, reduction of drug prices and promotion of generic prescribing and substitution. Governments are usually prepared to pay for new innovative medicines, but recommend cheaper generic equivalents for medicines with expired patent protection.

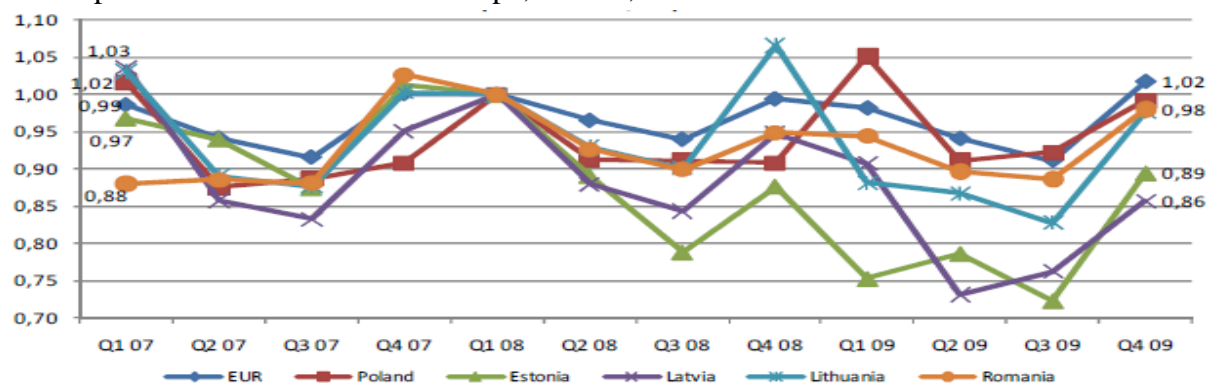
Results and discussion: The World Health Organization has recently analyzed the effects of the financial crisis on global pharmaceutical prices, expenditure and use during 2007-2009. Interestingly, the use of medicines, as well as their prices and spending, have increased in all WHO regions, except in Europe, and particularly in the Baltic countries. (Graph 1, 2). However, branded and patent protected medicines have still been used more than generic medicines during this period. Another study focused on pharmaceutical legislation implemented in 8 European countries during 2008 – 2011. Economically more stable countries (Austria, Estonia, Finland) have implemented fewer regulatory changes than less stable ones (Greece, Ireland, Spain, Slovakia, Portugal). Most of the strategies aimed to reduce public expenditure on medicines by increasing private spending, changing mark-ups and reducing medicines prices. Only few strategies have been based on generic prescribing and substitution (positive list, generic prescribing and changed mark-ups in Greece 2012). Overall, the use of medicines in Europe have not decreased during current crisis, except for Greece and Portugal in regards to treatment of chronic diseases (ACE inhibitors, antidepressants).

Graph 1: Use of medicines (globally and WHO regions): 2007-2009



WHO regions: AFR - African region, AMR - American region, EMR - Eastern Mediterranean and Arabic region, EUR - European region, SEAR - South Eastern region, WPR - Western Pacific region

Graph 2: Use of medicines in Europe, Poland, Romania and Baltic countries: 2007-2009



Conclusions: During the economic recession, many regulatory measures have been designed to shift the financial burden from public budgets to patients' private spending. As a consequence, increased drug co-payments could reduce the use of medicines in times of financial difficulties and unemployment. On the other hand, the reduction of drug prices could have detrimental effects on access to medicines if pharmaceutical companies decide to withdraw their medicines from positive lists. It is necessary to follow up the possible effects of reduced access and use of medicines on population health status.

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P30

GENERIC AND THERAPEUTIC DRUG SUBSTITUTION

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Key words: generic drug substitution; therapeutic drug substitution; Croatia, clinical appropriateness; cost-minimization

Introduction: There is considerable debate concerning the place of generic (from a brand to generic product) and therapeutic substitution (switching to a cheaper product usually within the drug class, eg. statins, proton pump inhibitors, drugs that affect the rennin-angiotensin system). Generic substitution is promoted by the Croatian Health Insurance Fund in Croatia in the primary health care setting, and recently in the secondary healthcare setting by establishment of centralized drug procurement system. It is estimated that generics constitute 50% of overall drug consumption in Croatia. Therapeutic substitution is more contentious as direct evidence to support equivalence is lacking. However, the price differentials makes it an attractive application of cost-minimization analysis for the more efficient use of health resources.

Results and discussion: Here we explore the existing open questions taking into consideration the clinical appropriateness and safety of generic and therapeutic switching, from an individual patient perspective and health service perspective. Although substitution may affect individual patients, it might be a price worth paying given the opportunity cost associated with the use of medicines that are clinically no better than cheaper alternatives. However, tensions are created by the promotion of the concept of patients choice at the same time. We review clinical areas or drug types where brand prescribing may be considered preferable because of the possibility of therapeutic inequivalence or potential for confusion (eg. medicines with a narrow therapeutic window where there is evidence regarding the risk of adverse patient reaction or inadequate efficacy, vaccines, biosimilars).

Conclusion: Generic substitution is almost universally accepted as desirable and cost reducing. Therapeutic substitution, although not as widely accepted, allows also considerable cost savings to be made. The trade-of is patient choice vs. rational fund spending. Arguably, for any publicly funded healthcare system, the latter has to be the priority.

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P31

**IMPLEMENTATION OF SUPPLY CHAIN MANAGEMENT (SCM) IN
PHARMACEUTICAL COMPANY**

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Key words: SCM, master planning, production planning, key performance indicators.

Introduction: The project scope is implementation of SCM in planning processes, supporting the production planning and detailed scheduling as well as the network planning across the company's supply to optimally match supply and demand. At the start of the project, the most important key aspects of the company without implementation of SCM activities (named To-day situation) are: Four SAP R/3 systems, one Business planning and control system and one R/2 system; no central supply chain network planning was available; production planning and detailed scheduling of the manufacturing processes were performed in various stand-alone systems interfaced with local ERP systems; no central statistical forecasting system; key-performance indicators (KPI) measurements were not consistently defined and the complete business processes were rather complex, without uniquely defined responsibilities for core planning tasks like master planning and detailed scheduling. Evaluation of created To-be situation is made after one year of implementation of SCM activities on the KPI's: planning, resource's exploitation, production, distribution and customer's satisfaction with the same percent of contribution.

Results and discussion: Evaluation of To-day and To-be situation is made on following KPI's: Planning (contribution of 35% in final score), Resource's exploitation (contribution of 15% in final score), Production (contribution of 30% in final score), Distribution (contribution of 10% in final score) and Customer's satisfaction (contribution of 10% in final score). The planning processes in To-be situation are mapped to the following ERP and APS modules: Demand planning SAP APO DP, Master planning SAP APO SNP, Detailed scheduling AP APO PP/DS, Materials requirements planning SAP R/3 MRP, Production order management SAP R/3 PP-PI, Inventory management AP R/3 IM-WM, Procurement direct materials SAP R/3 MM, Master

data management SAP R/3 MM, Supply chain controlling SAP R/3CO and SAP BW. The production plan is generated automatically by APO PP/DS which mine: reduction of machine set-ups, production of sequence ordered by increasing compound concentration, production sequence grouped by product and ordered by increasing order quantity. In case of bulk material, the holding tank has to be emptied as soon as possible, requiring to group products consuming the same bulk material. SCM implementation in the studied pharmaceutical company resulted in improvement in all defined KPIs (Fig.1). The highest improvement of 0,52% is for planning proces. If it is known that to the planning process were given 35% of factor of importance for the improvement of the company, then it can be concluded that the SCM implementation have allowed improvement in the most important part of the functioning of the studied pharmaceutical company.

Fig. 1. Comparative results before and one year after implementation of SCM activities

| | <i>To-Day situation</i> | | <i>To-Be situation</i> | |
|---------------------------|-------------------------|--------------------|---------------------------|--|
| <i>KPI</i> | <i>Score</i> | <i>Score</i> | <i>KPI</i> | |
| Planning | 0,79 | 1,31 | Planning | |
| Resource's exploitation | 0,34 | 0,45 | Resource's exploitation | |
| Production | 0,66 | 1,02 | Production | |
| Distribution | 0,25 | 0,3 | Distribution | |
| Customer's satisfaction | 0,3 | 0,35 | Customer's satisfaction | |
| <i>Final score</i> | <i>2,34</i> | <i>3,43</i> | <i>Final score</i> | |

The results shown that the parameter customer's satisfaction is with smallest improvement. That is owed to two factors, namely:

- 1.The presented data refer to the period in analysis of only one year (in all a relevant literature to evaluate the activities of SCM is said that the end score with a representative meaning can be obtained by been spent two years from the date of implementation of the SCM);
- 2.Clients like a end-users will need the longest period that is noted for improving the quality in the work of certain companies.

Conclusion: The visibility and problem solving capabilities of the entire organization improved by the use of a common data basis and a common visualization tool, allowing better and faster decisions. The master planning run enables the company to better foresee the future capacity issues and plan accordingly future investments. Collaborative demand planning with the customers allow for a proactive stabilization of the demand as changes in the demand by the customers are compared with a constrained demand from the previous master planning run and

exceptions are generated. By consolidating the system landscape, the IT maintenance costs were reduced significantly.

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P32

**COST-EFFECTIVENESS OF GLATIRAMER ACETATE FOR RELAPSIN-
REMITTING MULTIPLE SCLEROSIS
IN REPUBLIC OF MACEDONIA**

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Background: Multiple sclerosis, also known as MS, is a chronic disease that attacks the central nervous system, i.e. the brain, spinal cord and optic nerves. Over 2.5 millions people have MS worldwide and is typically diagnosed between ages 20 and 40. At present, six treatments are approved for patients with MS, including three interferon beta preparations, glatiramer acetate, mitoxantrone, and natalizumab. Glatiramer acetate is a synthetic protein that simulates myelin basic protein, a component of the myelin that insulates nerve fibers in the brain and spinal cord. This drug is given by subcutaneous injection every day for the treatment of relapsing-remitting MS. It is also used for patients who have experienced a first clinical episode and have MRI findings consistent with MS

Objective: To evaluate the cost effectiveness of four disease modifying treatments (interferon betas and glatiramer acetate) for relapsing remitting and secondary progressive multiple sclerosis in the Republic of Macedonia.

Methods: Cost-effectiveness and cost utility model was developed for analysis of multiple sclerosis treatment with two years time horizon (from a Republic of Macedonia payer perspective). The data used in development of the decision tree analysis model for pharmacological multiple sclerosis treatment were obtained from relevant randomized clinical studies. In the analysis only direct cost were included. Benefits and performance of medical treatments measured as QALY were extracted from published data. The price per dose was estimated and cost per QALY with 12% annual discount was calculated. Cost-effectiveness was evaluated using threshold of US \$ 31.500/QALY (EUR 24.040,17 /QALY) in RM.

Results: The direct costs of different available pharmacological therapy included in this model are presented in Table 1.

Table 1. Direct cost of Multiple sclerosis pharmacological therapy in R. Macedonia

FIRST MACEDONIAN AND FOURTH ADRIATIC CONGRESS ON PHARMACOECONOMICS AND OUTCOMES RESEARCH

| ATC | INN | Pharmaceutical Form | Јачина | Manufacturer | Package | Referent price per unit | Referent price per package | Packing for days | Montly treatment price (30 days) |
|---------|--|---------------------|---|--------------|---------|-------------------------|----------------------------|------------------|----------------------------------|
| L03AB07 | Interferon beta -1a AVONEX injection | Injection | 30mcg(6MIU)/0,5ml(SRJ) 30mcg(6MIU)/0,5ml (0,5ml) | BIOGEN IDC | 4 | 10,366.67 | 41,466.67 | 28 | 44,428.57 |
| L03AB07 | Interferon beta -1a REBIF 44 injection | Injection | 12MIU(44mcg)/0,5ml 12MIU(44mcg)/0,5ml | MERCK | 3 | 4,233.02 | 12,699.06 | 7 | 54,424.53 |
| | REBIF 44 injection | | 12MIU(44mcg)/0,5ml | | 12 | 4,233.02 | 50,796.23 | 28 | 54,424.53 |
| L03AB08 | Interferon beta -1b BETAFERON injection | Injection | 250mcg(8MIU)/ml 250mcg (8MIU)/ml (1,2 ml) | Bayer | 15 | 2,924.02 | 43,860.29 | 30 | 43,860.29 |
| L03AX13 | Glatiramer acetat COPAXONE | Injection | 20mg/1ml | TEVA | 28 | 1,360.71 | 38,100.00 | 28 | 40,821.43 |

The cost effectiveness of four disease modifying treatments (interferon betas and glatiramer acetate) for relapsing remitting and secondary progressive multiple sclerosis in the Republic of Macedonia are presented in Table 2 and 3

Table 2. Average cost per patient in R.Macedonia according to our pharmacoeconomic model

| Cost (EUR) | 1 | 2 | 3 | 4 |
|----------------------------|----------------------|----------------------|------------|--------------------|
| | IFNbeta 1a (30 mcg) | IFNbeta 1a (44 mcg) | IFNbeta 1b | Glatiramer acetate |
| | 380,307.99 | 467,698.81 | 382,734.49 | 350,818.83 |
| Incremental cost (1vs4) | | 29,489.16 | | |
| Incremental cost (2vs4) | | 116,879.99 | | |
| I Incremental cost (3vs4) | | 31,915.66 | | |

Table 3. Cost – effectiveness of Glatiramercetat in comparasion with other available pharmacological treatments of multiple sclerosis in Republic of Macedonia

| Comparasion of available pharmacological tretmans | Cost per QALY |
|---|---------------|
| (1 vs 4) | 79,700.44 |
| (2 vs 4) | 417,428.52 |
| (3 vs 4) | 177,309.24 |
| (1 vs 4) | 499,816.34 |
| (2 vs 4) | 2,850,731.39 |
| (3 vs 4) | 797,891.60 |

Conclusion: Glatiramercetat in monotherapy alone is a cost-effective treatment option for the prevention of relapses in patients diagnosed with RRMS in Republic of Mecedonia.

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P33

**THE COST-EFFECTIVENESS ANALYSIS OF THE LEVONORGESTREL-
RELEASING INTRAUTERINE SYSTEM (LNG-IUS) FOR THE TREATMENT OF
IDIOPATHIC HEAVY MENSTRUAL BLEEDING IN REPUBLIC OF MACEDONIA.**

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Key words: Cost- effectiveness, levonorgestrel LNG-IUS, menagerie treatment, heavy menstrual bleeding

Background: Dysfunctional uterine bleeding (DUB) is irregular bleeding that occurs in the absence of recognizable pelvic pathology, general medical disease, or pregnancy. Idiopathic heavy menstrual bleeding clinically defined as greater than 80 mL of blood loss per menstrual cycle, affects 10-30% of women and has negative influence on their health and quality of life.

Objectives: Our objective was to evaluate the cost-effectiveness of Levonorgestrel-releasing intrauterine system-LNG-IUS in comparison with combined oral contraceptives (OC) in treatment of heavy menstrual bleeding.

Methods: Cost-effectiveness and cost utility model was developed for analysis of menorrhagia treatment with one year time horizon (from a Republic of Macedonia payer perspective). This pharmacoeconomic model is designed for estimation of the DUB and essential menorrhagia alternative treatment costs in population of 1000 patients. The data used in development of the decision tree analysis model for pharmacological menorrhagia treatment were obtained from relevant randomized clinical studies. In the analysis only direct cost were included because the indirect costs associated with implementation of the LNG-IUS, as well as the cost of side effects treatment for both combined OC and LNG-IUS, are negligible. Benefits and performance of medical treatments measured as QALY were extracted from published data. The price per dose was estimated and cost per QALY with 3% annual discount was calculated. Cost-effectiveness was evaluated using threshold of US \$ 31.500/QALY (EUR 24.040,17 /QALY) in RM.

Results: A total accumulated cost per patient was 87,885 EUR for combined OC vs. 38.462 EUR for LNG-IUC. Literature search results didn't confirm differences in quality of life between the two compared groups. Incremental cost per patient gained for LNG-IUC is 48.423.

Conclusion: LNG-IUS treatment has better incremental cost-effectiveness ratio in comparison to combined OC treatment. On the other hand it is also certified that LNG-IUS treatment delays the hysterectomy for the period of 5 years in almost 60% of women with menorrhagia. As LNG-IUS has better treatment outcome, lower ICER and is not invasive surgical intervention it should be considered as first line treatment for the heavy menstrual bleeding.

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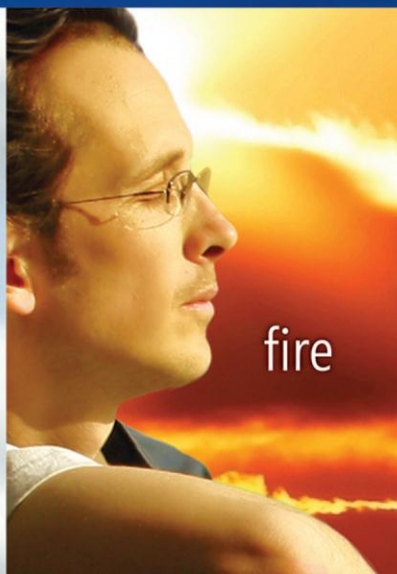
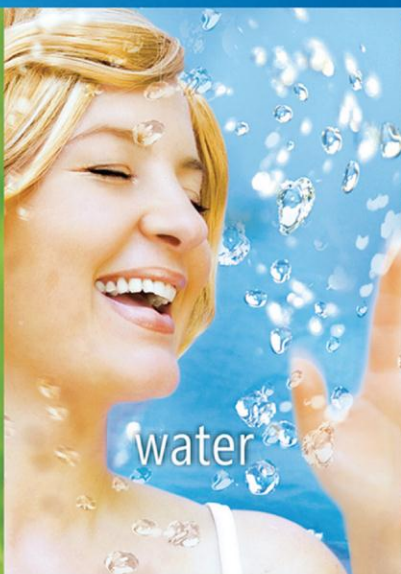


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