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Budget Impact of Introducing Linagliptin into Bosnia and Herzegovina Health Insurance Drug Reimbursement List in 2016-2018

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ABSTRACT

Introduction: Diabetes is reaching epidemiological scales worldwide. Beside health implications diabetes bears significant financial impact on health systems. Different treatment options aiming to prevent diabetes complications are available. Dipeptidyl-peptidase-IV (DPP-4) inhibitors like linagliptin are usually add-on therapy to metformin in order to achieve glycemic control. Expenditure for oral antidiabetic medicines in Bosnia and Herzegovina (B&H) is low accounting for only 2.53% of the total drug market expenditure. Linagliptin is not reimbursed in B&H mainly due to its perception of high cost medication. **Aim:** To assess budget impact (BI) of introducing linagliptin into health insurance reimbursement list in B&H through development of the budget impact model (BIM). **Material and methods:** Budget impact model was developed using Microsoft Excel 2010 based on current legislation and practice in B&H. Local epidemiology data and data on drug consumption from government reports in 2014 were used. Two scenarios with three-year time horizon have been developed: 1) without and 2) with linagliptin reimbursed and compared. **Results:** Inclusion of linagliptin into reimbursement list in Canton Sarajevo and Canton Tuzla would have positive budget impact on national level of B&H resulting in total savings of 18,194€, 235,570€ and 699,472€, in 2016, 2017 and 2018, respectively. **Conclusion:** Introduction of linagliptin into reimbursement list would decrease total costs for DPP-4 inhibitors and is favorable for positive decision on reimbursement in B&H. Applying BIM in decision making would assure better allocation and planning of resources at any region or administrative level in B&H.

Keywords: budget impact, linagliptin, pharmacoeconomics, reimbursement, diabetes, DPP-4 inhibitors.

1. INTRODUCTION

Diabetes, reaching epidemic proportions worldwide and typically occurs after the age of 40 years (1) where 90% of patients suffering from diabetes mellitus type 2 (DMT2) (2). International Diabetes Federation (IDF) estimates that 59.8 million persons are affected of which 9.1% population aged 20-79 years with 23.5 million undiagnosed patients (3). It is estimated that 1.5 million people with diabetes died in 2012 and more than 80% of diabetes deaths occur in low- and middle-income countries, which Bosnia and Herzegovina (B&H) belongs, according to the International Classification of Diseases (ICD) classification (4, 5).

It is estimated by the diabetes associations in Bosnia and Herzegovina that more than 220.000 people suffer from diabetes and majority are patients with type 2 diabetes (6). At least half of patients with type 2 diabetes have not been diagnosed and are unaware of (7). According to the data from 2010, almost 50.000 people with diabetes have been registered in the Federation of Bosnia and Herzegovina. In the B&H entity Republic of Srpska, there are about 60.000 patients, of which 15.000 are on insulin therapy (6). Number of diabetes patients in Bosnia and Herzegovina is increasing (8).

The results of studies in the Federation of B&H showed that 9.6% of the population older than 18 years of age reported at any time in the life has been diagnosed with diabetes, where over half of the population older than 18 years (21.7%) with blood sugar levels equal or higher than 6.1 mmol/l.

According to the Register of diabetes mellitus in the Federation of B&H entity Republic of Srpska total number of registered patients in 2013 was 41.248 and 30.010 (73%) of these were DMT2 (9).

Table 1 represents overview of diabetes type 2 epidemiology in Federation of B&H across regions.

Beside health complications, diabetes significantly impact on health care costs. In most EU countries, the cost of diabetes represents more than 10% of total healthcare costs (10). CODE-2 study indicates that approximately 75% of the costs for the treatment of DM refer to the cost of treating chronic complications; while the lowest share are the costs of medicines to treat diabetes (11). According to these study findings, 55% of the cost of treatment of diabetes mellitus refers to the hospitalization, while the medicines for the treatment of diabetes account for only 7% of the total cost of diabetes treatment.

Observing B&H neighboring countries, Serbia potentially allocates 222 million euros for the treatment of type 2 diabetes, of which 38 million for the control of diabetes with medication and over 180 million euros for the treatment of complications. If indirect costs (reduction of productivity and absence from work due to illness, unemployment and loss of productivity due to early death) account for approximately 30% of total costs are added to this figure, it can be estimated that in 2013, diabetes cost in Serbia were about 348 million euros (12).

In Croatia, based on data from the National Registry of people with diabetes–CroDiab cost of illness study showed that, 85.72% of all costs are related to diabetes complication treatment with 23.50% of direct costs related to oral antidiabetics and insulins (13).

Data on the costs of diabetes and its complications in B&H does not exist. According to the Report on drug utilization in B&H in 2014, share of antidiabetic drugs is extremely small, amounting to only 2.53% or 20.5 million euros (14).

The treatment of hyperglycemia in DMT2 begins with diet, nutrition education, physical activity and the attempt to reduce body weight in obese and overweight subjects. When these measures fail, therapy starts with oral hypoglycemic agents, mainly with metformin monotherapy, and if diabetes is uncontrolled after three months of therapy additional medicines should be considered. The main treatment goal is the control blood glucose levels, in order to prevent complications. The most important risk factor for the development of microvascular and macrovascular complications is inappropriate metabolic regulation of the disease and its improvement is reflected in the reduction of glycated hemoglobin (HbA1c) which is associated with a reduced risk of developing above mentioned complications (15, 16). Every 1% drop in HbA1c reduces the risk of microvascular complications by 40% and death by 21% (17).

The guidelines of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) for the treatment of type 2 diabetes, are directed to individual treatment of patients, taking into account the patient's needs and values (18, 19). The new guidelines recommend different target HbA1c, but still for majority of patients reduction of HbA1c <7% is recommend.

Metformin remains the initial treatment of choice and guidelines recommend adding, rather than changing to, additional agents when metformin no longer provides adequate glycemic control. Although metformin is highly effective in controlling blood glucose, the study published in 2010 showed that 17% of patients experienced failure within a year (20).

The choice of which agent(s) to add to metformin depends

on the advantages and disadvantages of the other therapies such as cost, risk and degree of hypoglycemia, adverse event profile, other comorbidities or patient preferences (18, 19).

Recommended agents to add to metformin are, a GLP-1 agonist, a dipeptidyl peptidase-4 (DPP-4) inhibitor, thiazolidinedione, meglitinide or sulfonylurea. This selection sequence is based on overall efficacy, risk of hypoglycemia, and effects on weight (21).

DPP-4 inhibitors have become important oral antidiabetic agents as second line therapy when patients do not reach their glycemic targets with metformin alone or as first line therapy when metformin is not tolerated or contraindicated (22). The DPP-4 inhibitors are a viable option in patients with mildly elevated A1c despite metformin therapy, especially when postprandial hyperglycemia is a predominant issue. The tolerability, route and frequency of administration and weight neutrality of DPP-4 inhibitors make them an attractive option compared with other DMT2 agents. Limitations of their use include cost and the inability to continually dose adjustments to optimize glycemic control. Linagliptin offers the advantage of not requiring a dose adjustment when used in patients with kidney impairment (23, 24).

As already mentioned, consumption of oral antidiabetics (OAD) is rather low in Bosnia and Herzegovina, and cost for this group of drugs are mainly driven by metformin. Table 2 gives an overview of total cost in euro for OAD consumption per ATC group and share in total drug consumption in 2014.

Key issue in access to novel groups of OADs like GLP-1 and DPP-4 is reimbursement status and health insurance coverage of costs for these medication which directly refers to its market share and prescribing (25, 26).

According to the current legislation regulating reimbursement approval, budget impact and other pharmacoeconomic parameters should be presented to Ministry of Health or Health insurance funds upon submission for reimbursement. Unfortunately these criteria are not taken into consideration in practice (27-29).

Hence, budget impact analysis of introducing linagliptin into reimbursement lists in Bosnia and Herzegovina was created, as a role model for more transparent decision-making process and under conditions that are proposed by current legislation.

2. MATERIALS AND METHODS

Budget impact model (BIM) was developed using Microsoft Excel (Microsoft Corp., Redmond, WA) version 2010. The model was used to assess the financial impact to health insurance funds (institutes) of introducing linagliptin into reimbursement lists of Federation of Bosnia and Herzegovina two major cantons (Canton Sarajevo and Tuzla) and the entity Republic of Srpska.

Canton Sarajevo and Canton Tuzla were selected, representing majority of inhabitants in Federation of Bosnia and Herzegovina. B&H Federation is a decentralized country, with each region as administrative unit and it's own health insurance fund financing medicines through reimbursement lists that are revised annually.

The model has been built according to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines (30) and existing legislation (31).

Only DPP-4 inhibitors registered and available in Bosnia and Herzegovina were taken into account, while categories of drugs for T2DM available in the market are excluded from this model. Only direct comparators of linagliptin, like sitagliptin and vildagliptin, are considered, as they are currently included into reimbursement lists and are universally recognized as similar in terms of safety and efficacy (32).

This analysis was conducted with a 3-year time horizon considering year 2016 as baseline. Using real market data we have calculated number of patients and corresponding consumption in packs on a yearly basis according to defined daily drug dose (DDD) (33). Two scenarios for the following years (2016-2018) have been developed: Base case scenario based on a forecast of market consumption using current trends. An alternative scenario where linagliptin is introduced into reimbursement list and its market share consequently increased.

In the base case scenario, the evolution of the market within three-year period (2016-2018) was observed with overall growth in consumption DPP-4 at an annual rate of 3% in terms of number of patients, as a direct result of increased prescription and availability of treatment in terms of inclusion in the positive list.

Alternative scenario considers the same criteria as a base case scenario plus introduction of the new DPP-4 inhibitor linagliptin into reimbursement list and market share uptake of 2%, 3% and 5% for selected time horizon, based on previous experiences and expert opinions. It should be noted that the market share of linagliptin is based on the overall market growth and proportional reduction of direct comparators which patients will be switched to the new therapy, meaning that the more patients treated with linagliptin, the fewer patients treated with the other drugs considered in the model. The reduction of the latter is proportional to the 2015 market share. For example, a 1% increase of linagliptin would mean a higher loss of patients (in percentage) for a drug having a higher market share, than for a drug having smaller market share. Budget impact of linagliptin is, therefore, simply the difference between costs relating to its increased use and costs relating to substituted drugs (alternative vs. base case scenario). Model calculates only direct costs of drugs that are included into reimbursement calculated per pack and annual consumption according to DDD. The drug costs on the basis of cost per pack of each drug, the number of days of therapy and the annual cost associated to each drug regimen was calculated.

3. RESULTS

Based on available epidemiology and pharmacoepidemiology data we have calculated number of patients treated with DPP-4 inhibitors in 2015 as presented in Table 3. Market trends and consumption of currently available DPP-4 inhibitors, sitagliptin and vildagliptin as referent scenario are presented in Table 4. As presented, consumption of DPP-4 is slightly increasing in observed period as well as corresponding costs based on price per pack. The highest consumption is registered in Canton Sarajevo, reflecting that these medicines are included into reimbursement lists so access is much higher than in other regions. Almost all of the costs are paid by health insurance funds/institute, and there is a low portion of out-of-pocket payment for these therapies. In base case scenario

Canton/Entity	Number of inhabitants	Prevalence (Morbidity/10.000 inhabitants)	Prevalence (%)	Number of diabetes patients
Una-Sana Canton	287.361	186.8	2%	5.368
Posavina Canton	28.669	350.2	4%	1.004
Tuzla Canton	499.144	323.2	3%	16.132
Zenica-Doboj Canton	397.813	313.6	3%	12.475
Bosnian-Podrinje Canton	32.390	350.1	4%	1.134
Central Bosnia Canton	252.573	300.1	3%	7.580
Herzegovina-Neretva Canton	224.029	380.9	4%	8.533
West Herzegovina Canton	81.527	142.8	1%	1.164
Sarajevo Canton	444.851	370.8	4%	16.495
Canton 10	78.365	91.2	1%	715
TOTAL Entity Federation of Bosnia and Herzegovina	2.326.722	280.97	3%	65.374
Total Entity Republic of Srpska	1.425.549	289.35	3%	41.248

Table 1. Prevalence of diabetes mellitus (ICD:E10-E14) across the Federation of Bosnia and Herzegovina administrative regions

ATC	Anatomical group	EUR	Share of total drug spending
A10	DRUGS USED IN DIABETES	20.845.671,02	7,67%
A10B	BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS	6.893.636,79	2,54%
A10BA	biguanides	3.679.675,61	1,35%
A10BA02	metformin	3679.675,61	1,35%
A10BB	Sulfonylureas	2.127.895,73	0,78%
A10BB12	glimpiride	1.514.884,73	0,56%
A10BB01	glibenclamide	577.605,93	0,21%
A10BB09	gliclazide	35.405,07	0,01%
A10BH	Dipeptidyl peptidase 4 (DPP-4) inhibitors	740.543,75	0,27%
A10BH01	sitagliptin	738.305,48	0,27%
A10BH02	vildagliptin	2.238,28	0,00%
A10BJ	Glucagon-like peptide-1 (GLP-1) analogues		
A10BJ02	liraglutid	313.102,97	0,12%
A10BX	Other blood glucose lowering drugs, excl. insulins	3.722,88	0,12%
A10BX02	repaglinid	3.722,88	0,01%
A10BF	Alpha glucosidase inhibitors	28.695,85	0,01%
A10BF01	acarbose	28.695,85	0,01%

Table 2. Overview of oral antidiabetic drugs consumption and share in total drug consumption in Bosnia and Herzegovina in 2014

in Table 5 market dynamics are presented if linagliptin is introduced into reimbursement lists in Canton Sarajevo and Canton Tuzla. As shown, the most impact is in Canton Sarajevo, which is expected since new drug takes market share of already available DPP-4 and in this region main competitors have the highest market share in Bosnia and Herzegovina. Linagliptin would cost 81,357€, 181,488€ and 223,280€ in

REGION	TOTAL POPULATION	PREVALENCE OF DIABETES	TOTAL NUMBER OF DIABETES PATIENTS	TOTAL NUMBER OF DMT2 PATIENTS TREATED WITH OAD	SHARE OF PATIENTS TREATED WITH DPP-4	NUMBER OF PATIENTS TREATED WITH DPP-4
Bosnia and Herzegovina	3.752.271	3%	106.622	77.834	3,40%	2.646
Federation of Bosnia and Herzegovina	2.326.722	3%	65.374	47.723	3,07%	1.465
Entity Republic of Srpska	1.425.549	3%	41.248	30.111	0,07%	21
Canton Sarajevo	444.851	3%	16.495	12.041	10,50%	1.264
Canton Tuzla	499.144	4%	16.132	11.777	0,03%	4

Table 3. Epidemiology data for selected regions with estimated number of patients treated with DPP-4 inhibitors in 2015

REGION	DPP-4	Price per pack (EUR)	Cost of therapy per month (EUR)	2015e		2016		2017		2018	
				UNITS (PACK)	Cost of therapy (EUR)						
BiH	sitagliptin	38,74	38,74	35.087	1.359.105	38.596	1.495.015	42.455	1.644.517	46.701	1.808.968
	vildagliptin	19,59	39,19	301	11.795	331	12.974	364	14.272	401	15.699
	TOTAL (EUR)				1.370.899		1.507.989		1.658.788		1.824.667
FBiH	sitagliptin	39,26	39,26	25.279	992.372	27.807	1.091.610	30.588	1.200.771	33.646	1.320.848
	vildagliptin	19,59	39,19	255	9.992	281	10.991	309	12.091	339	13.300
	TOTAL (EUR)				1.002.365		1.102.601		1.212.861		1.334.147
RS	sitagliptin	35,56	35,56	1.223	43.484	1.345	47.832	1.480	52.615	1.628	57.877
	vildagliptin	19,34	38,68	35	1.354	39	1.489	42	1.638	47	1.802
	TOTAL (EUR)				44.838		49.322		54.254		59.679
CS	sitagliptin	38,89	38,89	20.761	807.368	22.837	888.104	25.121	976.915	27.633	1.074.606
	vildagliptin	19,90	39,81	1	40	1	44	1	48	1	53
	TOTAL (EUR)				807.407		888.148		976.963		1.074.659
CT	sitagliptin	38,90	38,90	18	700	20	770	22	847	24	932
	vildagliptin	19,62	39,25	40	1.570	44	1.727	48	1.900	53	2.089
	TOTAL (EUR)				2.270		2.497		2.747		3.021

BiH=Bosnia and Herzegovina; FBiH=Federation of Bosnia and Herzegovina; RS=Entity Republic of Srpska; CS=Canton Sarajevo; CT=Canton Tuzla

Table 4. Base case scenario (without linagliptin introduced into reimbursement lists) within selected regions

observed three-year period respectively on national Bosnia and Herzegovina level, or 73,012€ 156,456€ and 177,316€ in Canton Sarajevo as driver of cost for linagliptin.

The budget impact analysis results are shown in Table 6, comparing base case and alternative scenario of introducing linagliptin into reimbursement lists in Canton Sarajevo and Canton Tuzla, which have been selected as an example and role model. It can be noticed that introduction of linagliptin into the reimbursement list in Canton Sarajevo and Canton Tuzla would have positive budget impact on national level of Bosnia and Herzegovina as well in Canton Sarajevo resulting in total savings of funds allocated to DPP-4 inhibitors of 18,194€, 235,570€ and 699,472€ in 2016, 2017 and 2018, respectively. Savings are mostly in Canton Sarajevo and account for 16,266€, 211,969€ and 610,087€ in 2016, 2017 and 2018, respectively. On the other side, introduction of linagliptin in Canton Tuzla would lead to an increase of costs for DPP-4 inhibitors, ranging from 14,880€ in 2016, 47,376€ in 2017 to 88,018€ in 2018.

4. DISCUSSION

This study aimed to assess budget impact of introducing linagliptin into Federation of B&H reimbursement lists.

There are certain limitations that BIM encountered. Namely, due to the differences in budgets available to medicines, there are massive differences in access to medicines among cantons and entities (34). Current legislation regulating introduction and assessment of medicines that should be introduced into B&H Federation Cantonal reimbursement list across Federation of B&H proposes different criteria, and one of them is budget impact analysis (31). Unfortunately, there is no implementation of such rules causing lack of transparency in decision making process.

According to reimbursement lists in Bosnia and Herzegovina effective in 2014, DPP-4 inhibitors are underrepresented on the lists. Only sitagliptin and vildagliptin are reimbursed in Canton Sarajevo when observing Federation of B&H. This is consequently reflected on its market share as it is shown.

In this study BIM focused on Canton Sarajevo and Canton Tuzla, as a role model for similar analytic approach as a rule in future decision-making. However, there are wide differences in between Cantons in Federation if B&H.

Expected price decreases which could happen during reimbursement list revisions were not taken into account. The main reason for this is because there is no officially established rule on annual price decrease. In

REGION	DPP-4	Price per pack (EUR)	Cost of therapy per month (EUR)	2015e		2016		2017		2018	
				UNITS (PACK)	Cost of therapy (EUR)						
BiH	sitagliptin	38,74	38,74	35.087	1.359.112	36.296	1.405.931	34.725	1.345.100	31.858	1.234.027
	vildagliptin	19,59	39,19	301	11.795	291	11.407	300	11.764	250	9.805
	linagliptin	34,77	34,77			2.340	81.357	5.220	181.488	6.420	223.210
	TOTAL (EUR)				1.370.906		1.498.695		1.538.352		1.467.042
FBiH	sitagliptin	39,26	39,26	25.279	992.377	25.507	1.001.324	22.898	898.890	25.187	988.780
	vildagliptin	19,59	39,19	255	9.992	241	9.424	205	8.015	225	8.817
	linagliptin	34,77	34,77			2.340	81.357	5.220	181.488	6.420	223.210
	TOTAL (EUR)				1.002.370		1.092.105		1.088.394		1.220.806
RS	sitagliptin	35,56	35,56	1.223	43.484	1.345	47.832	1.480	52.616	1.628	57.877
	vildagliptin	19,34	38,68	35	1.354	39	1.489	42	1.638	47	1.802
	linagliptin	34,77	34,77								
	TOTAL (EUR)				44.838		49.322		54.254		59.679
CS	sitagliptin	38,89	38,89	20.761	807.372	20.737	806.442	18.311	712.087	15.042	584.962
	vildagliptin	19,90	39,81	1	40	1	44	1	48	1	53
	linagliptin	34,77	34,77			2.100	73.012	4.500	156.455	5.100	177.316
	TOTAL (EUR)				807.411		879.498		868.590		762.331
CT	sitagliptin	38,90	38,90	18	700	15	583	17	642	18	706
	vildagliptin	19,62	39,25	40	1.570	30	1.177	33	1.295	36	1.425
	linagliptin	34,77	34,77			240	8.344	720	25.033	1.320	45.894
	TOTAL (EUR)				2.270		10.105		26.970		48.024

BiH=Bosnia and Herzegovina; FBiH=Federation of Bosnia and Herzegovina; RS=Entity Republic of Srpska; CS=Canton Sarajevo; CT=Canton Tuzla

Table 5. Alternative scenario (with linagliptin introduced into reimbursement lists) within selected regions

REGION	DPP-4	2016		2017		2018	
		BASE CASE SCENARIO	ALTERNATIVE SCENARIO	BASE CASE SCENARIO	ALTERNATIVE SCENARIO	BASE CASE SCENARIO	ALTERNATIVE SCENARIO
BiH	TOTAL (EUR)	2.949.386	2.931.192	3.244.324	3.008.755	3.568.757	2.869.284
	COST DIFFERENCE (EUR)	-18.194		-235.570		-699.472	
FBiH	TOTAL (EUR)	2.156.511	2.135.972	2.372.162	2.128.714	2.609.379	2.387.689
	COST DIFFERENCE (EUR)	-20.540		-243.449		-221.690	
RS	TOTAL (EUR)	96.465	96.465	106.112	106.112	116.723	116.723
	COST DIFFERENCE (EUR)	0		0		0	
CS	TOTAL (EUR)	1.737.075	1.720.149	1.910.783	1.698.814	2.101.861	1.490.990
	COST DIFFERENCE (EUR)	-16.926		-211.969		-610.871	
CT	TOTAL (EUR)	4.884	19.764	5.372	52.748	5.909	93.927
	COST DIFFERENCE (EUR)	14.880		47.376		88.018	

BiH=Bosnia and Herzegovina; FBiH=Federation of Bosnia and Herzegovina; RS=Entity Republic of Srpska; CS=Canton Sarajevo; CT=Canton Tuzla

Table 6. Alternative scenario (with linagliptin introduced into reimbursement lists) within selected regions

practice, prices are set during negotiations with manufacturers under reimbursement list revision process. Prices of medicines analyzed are those already published or proposed by the manufacturer. One of the limitations of the study as well the fact that the model did not consider costs occurring from adverse events. We also did not take into the account discounting since three years is short term and there

would be no significant impact of discounting on the total results. Model is based on real world data on drug Bosnia and Herzegovina directly related to the number of patients treated each and is as accurate as the data report.

Several countries (e.g. Australia, Canada, Belgium, Croatia, Hungary, and Poland) require manufacturers to make a BIA to support applications for national or regional reimburse-

ment, mainly because they find it useful in assessing their sustainability with scarce financial resources and because it is less complex and more comprehensive than cost effectiveness analysis (35).

Applying BIA in decision making would assure better allocation and planning of resources at any region or administrative level in Bosnia and Herzegovina. Additionally, even BIA is mentioned in current legislation, more details on conducting such analysis submitted to health insurance funds/institutes should be given to assure standardization.

5. CONCLUSION

This study has shown that introduction of linagliptin into reimbursement list would decrease total costs for DPP-4 inhibitors already reimbursed in Bosnia and Herzegovina ranging from -18,194€ in the first year, -235,570€ in second year and -699,472€ in the third year in the period 2016-2018. It can be concluded that BIM show that linagliptin is favorable for positive decision on reimbursement. BIA is demonstrated as a suitable tool for more transparent reimbursement decisions, and it should be more extensively used in everyday practice during reimbursement submissions. Even though BIA is proposed as part of the Federation of B&H reimbursement dossier submission, it should be more precisely defined and standardized through official guidelines for conducting such analysis. Beside positive impact on budget, it is also important to stress that introduction of novel DPP-4 inhibitor linagliptin would provide more flexible prescribing options for patients under approved indication.

- **Conflict of Interest:** The authors declare that they have no conflict of interest.

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