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- ОПРЕДЕЛЕНИЕ ПОРОГА «ГОТОВНОСТИ ПЛАТИТЬ» ПРИ ОДОБРЕНИИ МЕДИЦИНСКИХ ТЕХНОЛОГИЙ В УСЛОВИЯХ РОССИЙСКОГО ЗДРАВООХРАНЕНИЯ, РАССЧИТАННОГО НА ОСНОВЕ ПАРИТЕТА ПОКУПАТЕЛЬНОЙ СПОСОБНОСТИ
- ОРИГИНАЛЬНЫЕ РОССИЙСКИЕ ФАРМАКОЭКОНОМИЧЕСКИЕ ИССЛЕДОВАНИЯ

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VALIDATION OF PREDICTIVE PHARMACOECONOMIC MODEL OF INTRODUCTION OF MEDICINAL PRODUCT IBRUTINIB INTO CHRONIC LYMPHATIC LEUKEMIA THERAPY PRACTICE IN THE TERRITORY OF THE RUSSIAN FEDERATION

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***Summary**: This document represents the results of validation of pharmacoeconomic model of introduction of medicinal product Ibrutinib into chronic lymphatic leukemia therapy practice within the programme of drug provision for patients with hemophilia, cystic fibrosis, pituitary dwarfism, Gaucher disease, malignant neoplasms of lymphoid, haematopoietic and related tissues, multiple sclerosis, as well as patients after transplantation of organs and/or tissues (hereafter referred to as '7 cost-intensive nosologies (7 CIN) programme'). Budget impact analysis demonstrated the possibility to provide all patients requiring Ibrutinib therapy without budget increase using only a part of savings within the programme during a period of 2016 – 2018.*

***Key words:** pharmacoeconomics, validation, chronic lymphatic leukemia (CLL), high risk group, Ibrutinib, modeling, budget impact analysis, predictive modeling, '7 cost-intensive nosologies (7 CIN)' programme, generic products. Model description*

The purpose of modeling using the method of pharmacoeconomic budget impact analysis was the search of possible ways of introduction of the medicinal product Ibrutinib into the structure of state purchases for a period of 2016 - 2018 within launched in 2008 '7 cost-intensive nosologies (7 CIN)' programme intended for treatment of patients having the diseases classified as cost-intensive nosologies, such as chronic lymphatic leukemia. Current List of medicinal products regulating the range of medicinal aid within the programme was established by the Order of the Government of the RF No. 2782-p 'On approval of the list of vital, essential and necessary medicinal products on 2015 and the lists of drug products for medical use, and minimum range of medicinal products required for delivery of medical aid' dated 30.12.2014 [1].

Modeling horizon was 4 years (2015 - 2018). In this case the modeling itself was performed in 2 steps (Figure 1): 1) Prediction of future budget costs (Scenarios 1 - 2) on 2015 - 2018; 2) Budget impact analysis of introduction of the medicinal product Ibrutinib into the structure of state purchases within '7 CIN' programme (Scenarios 1.1 - 1.2 and 2.1 - 2.2).

Scenario 1 represents a prediction of budget costs with account of price reduction due to commercial distribution of generics for the following products (Table 1) within planning period.

Table 1 **Generics in '7 CIN' programme for a planning period [2,3]**

International non-proprietary name	Trade name	Market authorization holder	Registration date
Bortezomib	Boramilan® API	F-SINTEZ OJSC (Russia)	09.04.2014
	Bortezomib	'Biocad' OJSC (Russia)	12.01.2015
	Bartizar	'Sotex' Pharm Firm OJSC (Russia)	01.04.2015
Rituximab	Acellbia	'Biocad' OJSC (Russia)	04.04.2014
	Rituximab	'Biocad' OJSC (Russia)	04.04.2014
Imatinib	Genfatinib®	Laboratorio Tuteur S.A.C.I.F.I.A. (Argentina)	31.08.2010
	Philachromin® API	F-SINTEZ OJSC (Russia)	03.05.2012
	Imatinib Teva	Teva Pharmaceutical Works LTD (Israel)	28.09.2012
	Imagliv	Sandoz d.d. (Slovenia)	19.11.2012
	Neopax	'Krka-Rus' Limited Liability Company (Russia)	01.03.2013
	Imatib	'Pharm-Sintez' OJSC (Russia)	10.04.2013
	Gistamel	'Veropharm' Open Joint-Stock Company (Russia)	13.05.2013
	Imatinib	'Biocad' OJSC (Russia)	26.07.2013
	Imatinib TL	'Drugs Technology' LLC (Russia)	26.05.2014
	Imvec	PP 'Obolenskoye' OJSC (Russia)	08.10.2014
	Imatinib Foresight	'Foresight' OJSC (Russia)	17.12.2014
	Imatinib	RCI Syntez OJSC (Russia)	13.01.2015
	Imatinib medak	Medac GmbH (Germany)	01.06.2015
	Imatinib	Atoll LLC (Russia)	06.07.2015

Patent protection for glatiramer acetate expires in September 2015.

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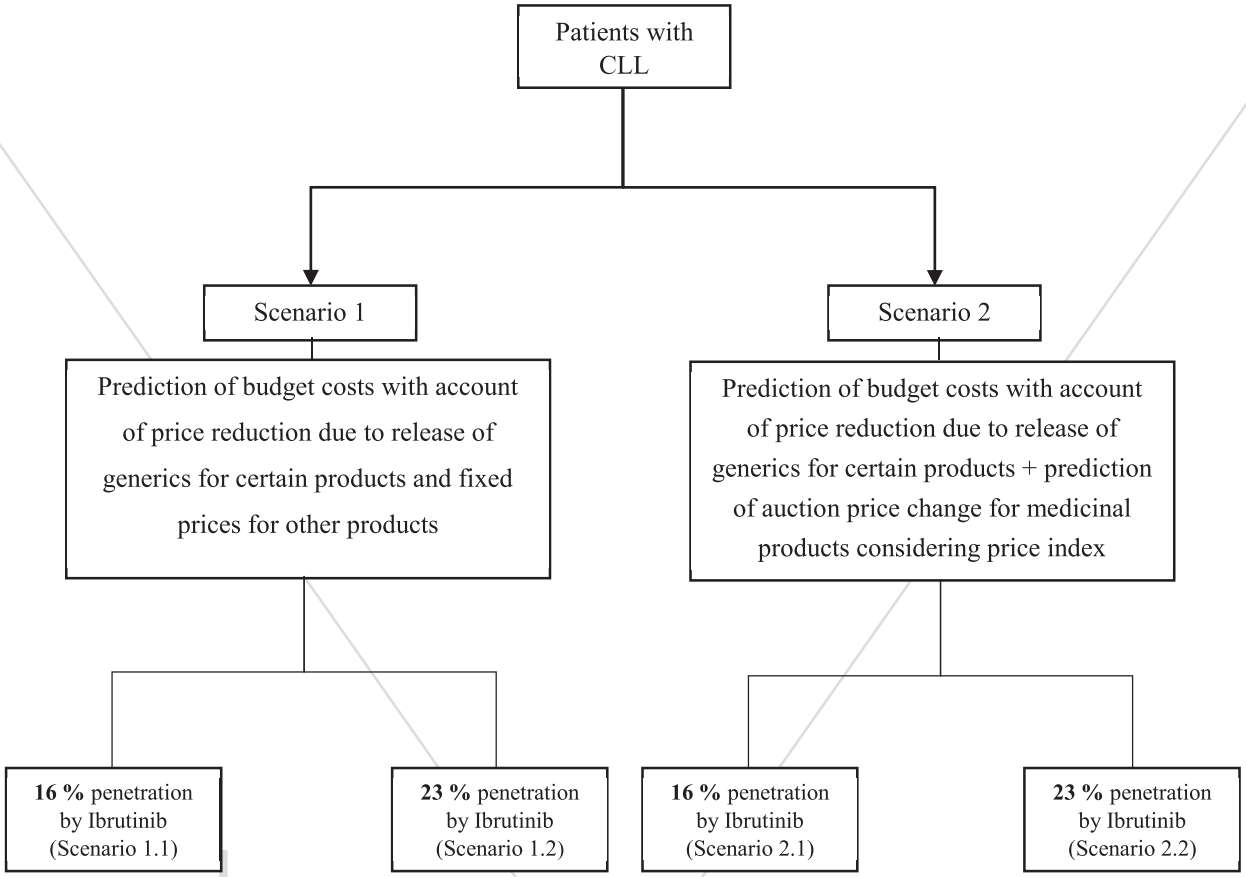

Figure 1. Study design

It should be noted that the prices of other products in Scenario 1 are fixed at auction price level of 2014 [4].

Considering price cut due to release of generics Scenario 2 also includes price forecast for other products. The forecast was performed using calculated annual average price index based on retrospective analysis of auction price formation (2012 - 2014) [4].

As per Russian clinical guidelines on diagnostics and treatment of lymphoproliferative diseases patients refractory to immunochemotherapy and falling under high risk group need Ibrutinib therapy. To fall under the group patient may meet the following criteria:

• Deletion 17p or mutation TP53 in patient having indications before the start of therapy.

• Relapse during 24 months after immunochemotherapy (FCR - Fludarabine, Cyclophosphamide and Rituximab). Observed in about 23 % of CLL patients (including 7 %, which cannot tolerate immunochemotherapy) [5,6].

Disease prevalence in 2013 was 6.9 cases per 100 000 residents (based on Rosstat data on January 1, 2015 Russia has just over 146 million permanent residents) [7,8]. It should be noted that 40 % of patients among them have slowly progressive CLL course, their life time being close to that for general population and this group has no need in immediate treatment initiation [5]. While, at average 20 % of CLL patients (16 % - 23 % depending on status) need initiation and/or continuation of Ibrutinib therapy. Using existing data one can calculate an approximate amount of patients falling under high risk group in territory of the RF (calculated as 20 %):

$$1\,460 \times 6.9 \times 0.6 \times 0.2 = 1\,209 \text{ patients.}$$

This model considers the analysis of Ibrutinib penetration. This analysis shows the amount of monetary resources, which will be necessary to introduce Ibrutinib into '7 CIN' programme for 16 % of patients (without those 7 %, who could not tolerate immunochemotherapy) or for the whole group of patients – 23 %.

Patients in high risk group can receive regimens of therapy with Fludarabine or Rituximab including combined therapy (Fludarabine + Rituximab) as prescribed by attending doctor. Besides that, therapy with Fludarabine or Rituximab is also prescribed in case of existing contraindications to one of the products [5]. The model assumes that the patients switched to Ibrutinib would not receive therapy of Fludarabine and Rituximab as 1:1, i.e. before switching to Ibrutinib one half of patients received Fludarabine therapy and the second half - Rituximab therapy.

Evaluation of the method used

Software chosen for modeling is a conventional environment for performing pharmacoeconomic analysis, since it provides sufficient transparency level of formula composition and allows to change purchased volume of products and their prices [9].

Pharmacoeconomic analysis comprises of 2 approaches of 'budget impact analysis', namely: 'optimization' and 'innovative'. The first allows to determine possible implementation scope of studied technologies based on such conditions of healthcare system as available budget and number of patients while meeting the requirement of total coverage of medical aid for all patients. The second approach determines the budget required to cover expenses on specified technology to achieve established target health parameters for target patient group [10, 11, 12].

This model represents an optimization approach of pharmacoeconomic analysis, i.e. offers a variant of implementation of innovative medicinal product for treatment of CLL patients within the approved budget of '7 CIN' programme. The objectivity criterion for this choice was limited amount of budget resources exceeding of which was undesirable.

Evaluation of the data used

Modeling of purchase structure for a planning period of 2015 - 2018 was based on published federal budget data and state purchases data.

Determination of financial capabilities of '7 CIN' programme budget in the planning period was based on budget data provided in Federal law No. 384-ФЗ 'On federal budget for 2015 and planning period of 2016 and 2017' dated 01.12.2014 [13].

The data of annual budget funds usage and average price of medicinal product package within '7 CIN' programme were based on the results of state purchases published at web portal http://zakupki.gov.ru [4].

Information on registration of generics was obtained from the site of national register of medicines http://grls.rosminzdrav.ru/ [2].

Prediction of future changes in prices of the products for which generics are planned to be released was based on the data of publication taken from digital resource http://imshealth.com/, which demonstrates dynamics of product price changes after release of generic analogues [14].

Results of pharmacoeconomic analysis

The data of predicted future budget costs demonstrated annual cost reduction within the planning period in each scenario (Table 2). Scenario 2 shows a bit more economy of budget funds due to descending trend of auction prices.

The 4 year prediction data demonstrates increased budget funds economy as compared to 2015 within the first and the second scenarios by 110 % and 141 %, respectively. In this case by the end of planning period the economy would be about 8.8 billion rubles within the first scenario and 9.9 billion rubles within the second scenario. It is expected that by 2018 the expenses for medicinal products used for treatment of oncohaematologic diseases within '7 CIN' programme would decrease by 3.5 billion rubles or 22 %.

The maximum effect on savings amount will have the reduction of medicine product prices due to commercial distribution of generic analogues within the programme that in its turn allows to use budget appropriations by implementation of innovative medicines.

Performed analysis demonstrated the possibility of introduction of Ibrutinib into the structure of state purchases within '7 CIN' programme in two scenarios without additional financing using only the part of savings. Besides that, additional economy was provided due to the fact that the patients receiving Ibrutinib will not receive Fludarabine and Rituximab within the program (Tables 3 - 4).

As is seen from Table 4, even at 23 % penetration charges for Ibrutinib in 2018 use less than a half of savings within the programme.

Comparative characterization using predicted values of savings in oncohaematology allowed to conclude that introduction of medicine product Ibrutinib into the structure of state purchases can be implemented due to economy obtained in oncohaematology without using the savings from other nosologies (Tables 5 - 6).

Table 2. **Prediction of '7 CIN' programme budget funds use**

Year	2015		2016		2017		2018	
Scenario No.	№1	№2	№1	№2	№1	№2	№1	№2
Budget target, billion rubles	44	44	44	44	44	44	44	44
Actual budget (including oncohaematology), billion rubles	39,8	39,8	38,2	37,8	36,7	35,9	35,2	34,1
Economy (overall programme), billion rubles	4.2	4.1	5.8	6.2	7.3	8.1	8.8	9.9
Charges in oncohaematology, billion rubles	16	16	14.8	14.8	13.7	13.7	12.5	12.5

Table 3. **Results of budget impact analysis as per Scenario 1**

Year	2016		2017		2018	
Penetration rate for Ibrutinib (part of patients, which will use the product), %	16	23	16	23	16	23
Planned amount of patients using Ibrutinib, persons	313	450	621	893	929	1335
Charges accounted for Ibrutinib, billion rubles	0,8	1,1	1,5	2,2	2,3	3,3
Economy (overall programme), billion rubles	5,8	5,8	7,3	7,3	8,8	8,8
Economy accounted for Fludarabine and Rituximab, billion rubles	0,12	0,17	0,22	0,32	0,3	0,4
Actual budget economy (including Fludarabine and Rituximab), billion rubles	5,9	6	7,5	7,6	9,1	9,3

Table 4 **Results of budget impact analysis as per Scenario 2**

Year	2016		2017		2018	
Penetration rate for Ibrutinib (part of patients, which will use the product), %	16	23	16	23	16	23
Planned amount of patients using Ibrutinib, persons	313	450	621	893	929	1335
Charges accounted for Ibrutinib, billion rubles	0,8	1,1	1,5	2,2	2,3	3,3
Economy (overall programme), billion rubles	6,2	6,2	8,1	8,1	9,9	9,9
Economy accounted for Fludarabine and Rituximab, billion rubles	0,1	0,2	0,2	0,3	0,3	0,4
Actual budget economy (including Fludarabine and Rituximab), billion rubles	6,3	6,4	8,3	8,4	10,2	10,4

Table 5 **Результаты анализа «влияния на бюджет» относительно экономии в онкогематологии согласно сценарию 1**

Year	2016		2017		2018	
Penetration rate for Ibrutinib (part of patients, which will use the product), %	16	23	16	23	16	23
Planned amount of patients using Ibrutinib, persons	313	450	621	893	929	1335
Charges accounted for Ibrutinib, billion rubles	0,77	1,1	1,52	2,19	2,28	3,27
Economy in oncohaematology, billion rubles	1,18	1,18	2,06	2,3	3,47	3,47
Economy accounted for Fludarabine and Rituximab, billion rubles	0,12	0,17	0,22	0,32	0,3	0,43
Actual budget economy (including Fludarabine and Rituximab), billion rubles	1,3	1,35	2,28	2,62	3,77	3,9

Table 6 **Results of budget impact analysis with respect to economy in oncohaematology as per Scenario 1**

Year	2016		2017		2018	
Penetration rate for Ibrutinib (part of patients, which will use the product), %	16	23	16	23	16	23
Planned amount of patients using Ibrutinib, persons	313	450	621	893	929	1335
Charges accounted for Ibrutinib, billion rubles	0,77	1,1	1,52	2,19	2,28	3,27
Economy in oncohaematology, billion rubles	1,2	1,2	2,32	2,32	3,47	3,47
Economy accounted for Fludarabine and Rituximab, billion rubles	0,12	0,18	0,23	0,32	0,31	0,45
Actual budget economy (including Fludarabine and Rituximab), billion rubles	1,32	1,38	2,55	2,64	3,78	3,92

Conclusion

Performed analysis of predictive pharmacoeconomic model for introduction of medicinal product Ibrutinib into CLL therapy practice in the territory of the RF demonstrated that the approach used complies with conventional international guidelines on performance of pharmacoeconomic studies.

The model demonstrates the possibility of introduction of medicinal product Ibrutinib into the structure of state purchases within '7 CIN' programme for planning period (2016 - 2018) without the need of budget increase and using only the savings accumulated due to price reduction for programme products associated with commercial distribution of generics. Introduction of Ibrutinib will require to use only a part of savings leaving the possibility of further program optimization due to additional economy for increasing the number of patients receiving a therapy with innovative medicinal products, which commercial distribution has already started or will be started in the period of 2016 - 2018.

References

1. Order of the Government of the RF No. 2782-p 'On approval of the list of vital, essential and necessary medicinal products on 2015 and the lists of drug products for medical use, and minimum range of medicinal products required for delivery of medical aid' dated 30.12.2014.
2. State Register of Medicines [Digital resource]. – Access mode: http://grls.rosminzdrav.ru/
3. Drug discovery & development [Digital resource]. – Access mode - http://www.dddmag.com/news/2015/01/supreme-court-sides-teva-drug-dispute Accessed date: 02.07.2015.
4. Official internet site of the Russian Federation for providing information on orders placed for product supplies, performing works and rendering services [Digital resource]. – Access mode: http://zakupki.gov.ru/
5. Russian clinical guidelines on diagnostics and treatment of lymphoproliferative diseases. Under the supervision of Professor I.V. Poddubnaya, Professor V.G. Savtchenko, M.: MMA MediaMedica, 2014. – P. 68: Fig.
6. Resolution of the Expert Council 'Availability of oncology disease treatment in the Russian Federation' dated 17.04.2015.
7. B.A. Bakirov, D.O. Karimov, A.B. Bakirov. Epidemiological studies of chronic lymphatic leukemia, Palmarium Academic Publishing, 2015.
8. Federal State Statistical Service [Digital resource]. – Access mode: http://www.gks.ru/
9. R.I. Yagudina, A.Yu. Kulikov, E.E. Arinina. Pharmacoeconomics in oncology. M.: 'Shiko' OJSC, 2011. – 568 P.
10. R.I. Yagudina, V.G. Serpik. On the possibility to combine 'budget impact' and 'cost-effectiveness' analyses - creation of '3D' pharmacoeconomic model. Pharmacoeconomics: theory and practice, 2014; Vol. 2, No. 3, P. 4 - 13.
11. A.Yu. Kulikov, M.M. Litvinenko. Methodological principles of modeling in pharmacoeconomic studies: various levels of complexity and various values of obtained results. Pharmacoeconomics: theory and practice, 2014; Vol. 2, No. 2, P. 9 - 22.
12. R. Yagudina A.Yu. Kulikov. Theoretical basis of pharmacoeconomic method: budget impact analysis // Pharmacoeconomics. Advanced pharmacoeconomics and pharmacoepidemiology. 2011. No. 2 , P. 9 - 12.
13. Federal law No. 384-ФЗ 'On federal budget for 2015 and planning period of 2016 and 2017' dated 01.12.2014.
14. Mia Reinwald, Patentklippe 2016 //IMS Health, 03.2015 [Digital resource]. – Access mode: http://www.imshealth.com/deployedfiles/imshealth/Global/EMEA/Germany_Austria/Press%20Room/IMS%20Articles/2015/2015_03_PharmaRelations_Patentklippe2016.pdf