

Trend Analysis of Combined Drugs Creation (for Example Acetylsalicylic Acid)

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Abstract: The pharmaceutical market of Ukraine in January 2015 was registered 71 drug based acetylsalicylic acid (ASA), for which 52% combined. The most common combinations of ASA with acetaminophen and caffeine (45.9%), magnesium hydroxide (18.9%), bisoprolol (10.8%), ascorbic acid (8.1%), clopidogrel (5.4%). Comparing markets combined drugs ASA of Ukraine, the Russian Federation, 28 EU countries, Norway, Switzerland, India, Syria, Australia and the USA identified the active pharmaceutical ingredients, combined with ASA in a single dosage form. The analysis of questionnaires 40 pharmacists pharmacies Ternopil, Khmelnytsky and Kyiv regions of Ukraine noted that the biggest demand is mono-drugs ASA, Citramon, Askofen and Cardiomagnyl. Methods of pharmacoeconomic studies proved efficient use Upsaryn UPSA with vitamin C tabl. spike. tuba in box number 20 BMS (France), Citramon tablets number 6 PJSC "Monfarm" (Ukraine) and Cardiomagnyl tabl. film-coated shell 75 mg in bottle number 100 Nycomed Austria (Austria). On the basis of six State Forms of drugs in Ukraine (2009-2014) was found that the combination of drugs based on ASA is recommended to use of ascorbic acid (Aspiryn® C, Asprovit C, Upsarin UPSA with vitamin C), dipyridamole (Agrenox®), magnesium hydroxide (Cardiomagnyl, Cardiomagnyl Forte). Some of the standard combination of ASA (combination of paracetamol and caffeine) are not in form. For optimize State Form of drugs by improving health system in Ukraine can be useful pharmacoeconomic analysis of combination therapies with the current official system to note the combination of ASA with statins, esomeprazole, isosorbide.

Key words: Acetylsalicylic acid, combined drugs, supply and demand, pharmacoeconomic research, formular.

1. Introduction

Currently the main indication for use of ASA (acetylsalicylic acid) is also inflammation, especially rheumatism, rheumatoid arthritis and arthrosis, infectious-allergic myocarditis and so on. It is also used as a medicine for pain syndromes of various origins such as neuralgia, sciatica, migraine, cold and so on [1].

To date only Antiplatelet agents, whose effectiveness proved by numerous clinical studies are managing [2, 3]. It remains the "gold standard" of antiplatelet therapy. In connection with antiplatelet properties of ASA prescribed to prevent postoperative

thrombosis, disorders of blood circulation of the brain to prevent stroke, people with chronic ischemic heart disease, including patients with myocardial infarction [4, 5].

Today ASA is part of more than 400 drugs dispensed without a prescription. There are more than 50 trade names of drugs. Annual consumption of drugs containing ASA exceeds 40 billion. Tablets, including German pharmaceutical companies produce more than 50 thousand [6].

Interaction with other drugs that are used in conjunction with ASA, could lead to the strengthening or weakening of the therapeutic effect or unwanted action of these drugs. ASA potentiates [7, 8]:

- therapeutic effect of anticoagulants (coumarin derivatives and heparin);
- the impact of corticosteroids for their oral administration;

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- the risk of gastrointestinal bleeding in case of simultaneous use of corticosteroids or alcohol;
 - concentration of digoxin, barbiturates and lithium plasma;
 - therapeutic effect of oral hypoglycemic agents sulfonylurea class;
 - therapeutic and adverse effects of NSAIDs, methotrexate, and reserpine fenitoina;
 - the effect of antimicrobial sulfonamides including co-trimoxazole;
 - the effect of triiodothyronine.
- ASA inhibits actions [8, 9]:
- aldosterone antagonist (spironolactone, kanreonat);
 - diuretics (furosemide);
 - antihypertensive agents and antypodagric and hypouricemic drugs (probenecid, sulfinpyrazone).

Recently the market appeared combined medicinal products based ASA. They are characterized by high pharmacological effect and accordingly broader indications for use. The aim of this study was to analyze the main trends create of combined drugs ASA and appropriateness of their use of pharmacoeconomics position.

2. Materials and Methods

The indicators characterizing the state of the market, including proposals related portfolio of medicines and price trends.

To analyze the product range used by the State Register of medicines Ukraine [10], which includes all registered drugs. For the study used data for January 2015.

Pricing policy of pharmaceutical companies in the domestic market combined drugs ASA characterized by changing of liquidity ratio, solvency adequacy ratio and accessibility ratio for combined preparations of acetylsalicylic acid in the period from January to February 2015 [11].

The liquidity ratio for (Rliq) calculated by the formula:

$$Rliq = (C_{max} - C_{min}) / C_{min},$$

where C_{max} —the highest price of the drug on the market;

C_{min} —the lowest price of the drug.

Said ratio shows the ratio between the maximum and minimum price of a particular drug in a certain period of time and in a particular market. Liquidity ratio price may be in the range of 0.1 to 1.0 and above. If this ratio is 0.5 or higher, which means that the price fluctuations of between 50% and higher. When liquidity ratio exceeds 1.0, it means that the range of the price of the medicinal product is characterized by more than one hundred percent difference. Based on the concept of social-ethical marketing, the essence of which is the study of consumer needs and meet them more effectively than the competition, and taking into account the welfare of all members of society, the liquidity ratio for the wholesale segment of the domestic pharmaceutical market from 0.16 to 0.5, and especially from 1.0 is not valid and is not ethical because ultimately it affects the patient.

To assess the impact on the value of demand in the purchasing power of medicines a patient is advisable to count as an indicator of solvency adequacy ratio (Ras). This indicator is the ratio scale drug prices for the month to the average monthly salary percentage, namely:

$$Ras = (C_{max} - C_{min}) * 100\% / W_a,$$

where Ras - solvency adequacy ratio;

W_a —average wages.

Pricing can analyze market conditions and such indicator as the availability ratio (Ra), which is calculated by the formula:

$$Ra = C / W_p - 1,$$

where C—average retail cost of the drug for a certain period, UAH;

W_p —average wages for a certain period, UAH [12].

For market research combined drugs in the world ASK searched lists of drugs 35 other countries through the Internet and available literature. In the

course of the analyzed segment markets of the Russian Federation [13], 28 EU countries, Norway, Switzerland, India, Syria, Australia and the USA [14-49].

In order to determine the demand for drugs combined ASA conducted a survey of pharmacists pharmacies Ternopil, Khmelnytsky and Kyiv regions. 40 pharmacists responded to 12 questions questionnaire and after reviewing the list of medicines that are used in medical practice, compiled them in order of decreasing demand of patients [50].

In the article of collecting information on the Cochrane Library Clinical use of study drugs and calculation methods performed pharmacoeconomic analysis [51, 52]. To calculate costs using a weighted average retail prices of medicines in Ukraine in December 2014 [11].

To install the most efficient treatment regimen used methods of pharmacoeconomic analysis: costs minimization, cost-effectiveness and cost-utility.

Cost-minimization analysis-type of pharmacoeconomic analysis of election-related or drug treatment with minimal cost while equally therapeutic efficacy. The purpose of the analysis is to confirm the benefits of a cheaper method or medication that will save money. This analysis is used when possible to establish that the two alternative treatment regimens have similar effectiveness or drugs are bioequivalent activity.

Cost-effectiveness analysis-type of pharmacoeconomic analysis to assess the effects of treatment, and the economic value of pharmacotherapy. The main purpose of the cost-effectiveness method is to establish the treatment regimen to be most effective at the lowest cash expenses. The unit of cost-efficiency analysis is the cost-effectiveness ratio, which shows the cost per unit of effectiveness. It allows you to define the regimen that ensures greater efficiency at lower or equal to the cost of treatment. It is calculated by the formula:

$$CER = C / Ef,$$

where CER—ratio cost-efficiency;

C—cost for the treatment, UAH;

Ef—effectiveness of the treatment.

The lower the cost-effectiveness ratio, the smaller the amount necessary to obtain the effect of treatment.

Cost-utility analysis to evaluate changes in the quality of life of the patient, that patient studied opinion on the results achieved treatment rate determined by increasing the number of years of life, the quality and not the effectiveness of treatment regimens. This ratio CUR (cost-utility) is calculated by the formula:

$$CUR = C / Ut,$$

where Ut—rate benefit.

Defined utility ratio to evaluate treatment with minimal [53, 54].

For the purpose of comparative evaluation of government recommendations on rational prescribing drugs analyzed information on the combination of drugs based on ASA. Recommendations for management purposes and the use of drugs considering the efficiency, safety and economic feasibility of their use in medical treatment of diseases and conditions contained in the State logbook medicines that the experience of other countries in Ukraine annually published. State Form of medicines from 2009 wearing a recommendation, and since 2013 it approved by the Ministry of Health of Ukraine [55].

3. Results and Discussion

3.1 Marketing Researches of Acetylsalicylic Acid Combined Drugs in Ukraine

Preparations based ASA include three pharmacological groups: antithrombotic agents (B01), analgesics (N02), anti-inflammatory and antirheumatic drugs (M01) [56].

In Ukraine was registered 71 drug-based ASA, of which 52% combined [10]. The work established that in Ukraine there are often a combination of ASA with acetaminophen and caffeine (45.9%), magnesium hydroxide (18.9%), bisoprolol (10.8%), ascorbic acid

(8.1%), clopidogrel (5.4%). Present as single drugs dipyridamole with acetylsalicylic acid—Agrenox®; aminoacetic acid—Alka-Prym®; anhydrous citric acid, sodium bicarbonate—Alka-Zelttser®; phenylephrine bitartrate and hlordeniraminom maleate—Aspiryn® Complex. Chart ratio of drugs ASA with other active substances in Ukraine is shown in Fig. 1.

Medicines research group produced mainly in the form of tablets (73%), and 9 of drugs covered film membrane, and 5-effervescent tablets. Note that the combined coating film coated tablets ASA allows further reduce the ulcerogenic effect, and use of effervescent tablets-accelerate during the onset of therapeutic action. 24% of the combined drugs based on ASA have the form of capsules. Exclusive dosage form in the group is effervescent powder for oral solution, which is Aspiryn® Complex.

The vast majority (56.76%) combined preparations ASA made in Ukraine. Among domestic manufacturers occupy dominant positions LLC

“Pharma Start” by offering 6 medicines and JSC Pharmaceutical firm “Darnitsa”—4 drugs test group. PJSC “Fitofarm” PJSC “Kyiv Vitamin Factory” and JSC “Lubnypharm” offer the market 2 drugs. PJSC “Chempharmfactory Red Star”, JSC “Farmak”, JSC “Monpharm”, LLC Pharmaceutical company “Health”, JSC “Kievmedpreparat” produced 1 combination drug based on ASA.

The leading importers are Poland (13.5%), represented pharmaceutical factory “Polfarma” SA and Germany, which holds 10.8% and divided between Bayer Bitterfeld GmbH (2 drugs), Boehringer Ingelheim Pharma GmbH and Co. COG, mibe GmbH Artsnaymittel-1 offers. The share of imported drugs France (Bristol-Myers Squibb, Sanofi Winthrop Indastria) and India (Akums Drahs and Pharmaceuticals Ltd, Menr Farmasyutikalz Pvt. Ltd.) is around 5.4%, and Spain (Kern Pharma SL), USA (Novartis Konsyumer Halsey, Inc.) and Estonia (LLC “Vitale-HD”) provide one drug [57].

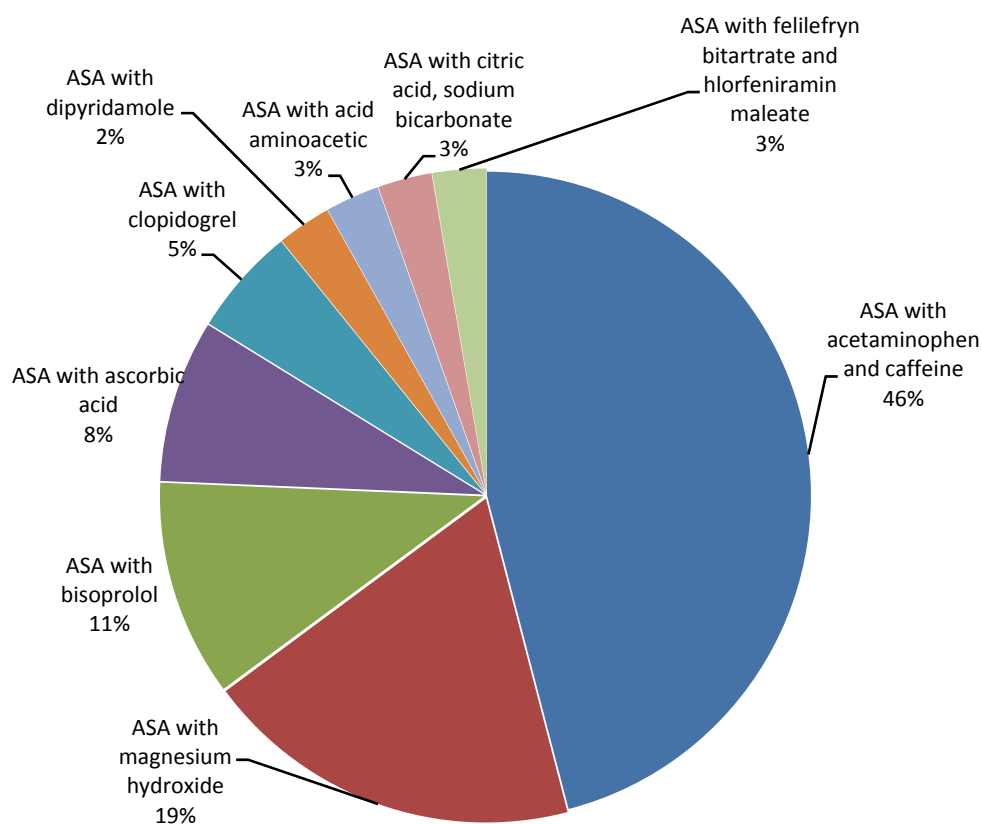


Fig. 1 Figure of the acid drugs aspirin with other active substances ratio in Ukraine.

To determine market saturation range of drugs ASA conducted a comparative analysis product range of pharmacies in city Ternopil (Ukraine). After analyzing the data, we can say that the leader of sales in Ternopil pharmacy is “Hello” and “Pharmacy 103”, where sales are 8 products based on ASA. In second place is the “Pharmacy 78” and “Your Sorcerer”. They offer 6 drugs test group.

The analysis of price conjuncture allowed to make conclude that fluctuations in the price of medicines does not exceed 50%. This indicates a slight difference in prices for drugs ASA, represented by different wholesalers. Thus, the lowest liquidity ratio of combined preparations ASA was in January 2015 ($R_{liq} = 0.008$) for Alka- Pym® effervescent tablets number 2x1, number 2x5 in a strip Pharmaceutical Plant “Polfarma” SA Poland, the highest ($R_{liq} = 0.125$) for Citramon-F tablets number 6 in contour cell packages PJSC “Fitopharm” Ukraine for February 2015.

Analyzing solvency adequacy ratio, obtained the following data: ASA drugs among the lowest it has been for Citramon F Forte capsules number 6 in a blister PJSC “Fitopharm” Ukraine (January $R_{as} = 0.008$, in February $R_{as} = 0.003$) and Farmadol® tablets number 10 in the blister JSC “Farmak” Ukraine (January $R_{as} = 0.009$, in February $R_{as} = 0.004$).

With availability ratio results judged on the purchasing power of drug users. The most accessible were: Citramon-F tablets number 6 in the contour cell packages PJSC “Fitopharm” Ukraine, Citramon-F Forte capsules number 6 in a blister PJSC “Fitopharm” Ukraine, Farmadol® tablets number 10 in the blister JSC “Farmak” Ukraine, which were availability ratios important 0.99 over the period.

Analysis of the marketing policy of pharmaceutical manufacturers combined preparations ASA suggests that domestic drugs distinctive two-tier distribution channel consisting of two middlemen—wholesalers and pharmacies. For foreign funds distinctive three-tiered channel. This three-tiered channel consists of the wholesale company importing wholesalers and

pharmacies. Most manufacturers of these drugs have chosen several intermediaries, is choosing intensive distribution of their medicines.

The leading suppliers of wholesalers are: Venta (Odessa), Farmplaneta (Lutsk), Lutskfarmatsiya (Lutsk), Ametryn (Kharkiv), Unipharma (Kyiv), BDM (Dnepropetrovsk), Optima Farm (Simferopol).

3.2 Analysis of Acetylsalicylic Acid Combined Drugs Market in Europe, Asia, Australia and America

In analyzing markets combined drugs ASA Ukraine, the Russian Federation, 28 EU countries, Norway, Switzerland, India, Syria, Australia and the United States of America was got the distribution of analyzed drugs on Fig. 2.

Analysis of the range of combined preparations revealed that ASA also combined with pravastatin (Pravastatin-Portugal, France), rosuvastatin (Rozucor ASP, Unistar-India), atorvastatin (A Vin AS, Aspivas, Atchol ASP, Atofast-AS, Aztor-ASP, CV Pill, Duocad, Lipicure AS, Liponorm-ASP, Lower A, Mactor ASP, Modlip ASP, Tonact ASP-India), atorvastatin and clopidogrel (Lipikind Plus, Noklot CV, Stagrel-AV-India), atorvastatin and ramipril (Trinomia-Spain, RIL-AA, Avopril AS-India), atorvastatin, metoprolol and ramipril (Zycad 4-India), hydrochlorothiazide, atenolol, ramipril and simvastatin (Polycap-India), esomeprazole (Axanum-Spain, Latvia, Portugal, Romania, Slovenia Hungary, Onnua-Italy), metoclopramide (Migramax-United Kingdom, Migpriv-Italy, Hungary, France), codeine phosphate (Boots Aspirin and Codeine Tablets BP, Dispersible Co-codaprin Tablets BP-United Kingdom, Codis®-UK, Australia, Kodimagnyl “DAK”-Denmark, Ascodan®-Poland, Disprin Forte®-Australia), codeine phosphate and magnesium hydroxide (Kodimagnyl Ikke-stoppende “DAK”-Denmark), codeine and paracetamol (Casfen, Gridor, Veganine-Portugal, Novacetol cp-France, Codopyrin-India), codeine and caffeine (Cofena, Dolviran-Portugal, Alnagon NEO-Slovak Republic,

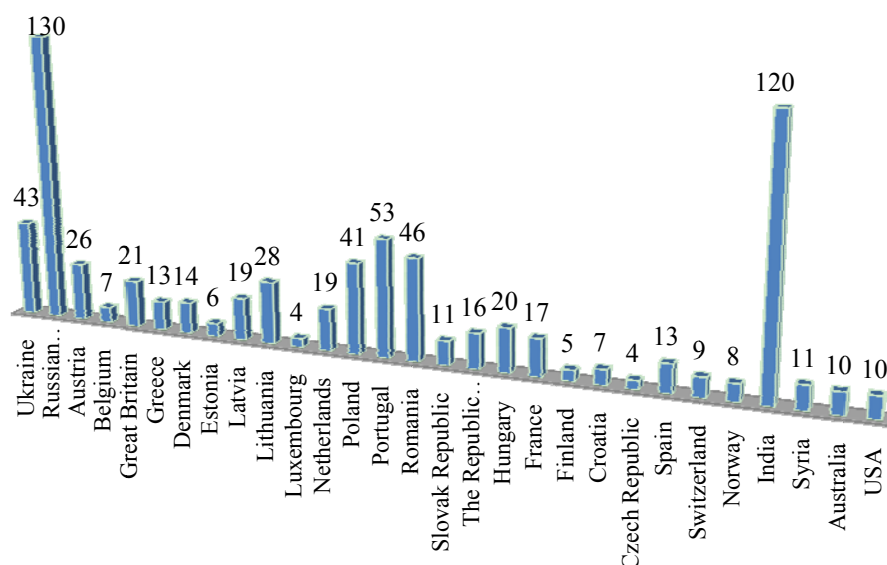


Fig. 2 Value of combined drugs acetylsalicylic acid in the analyzed countries.

Sedaspir cp-France), codeine, caffeine and paracetamol (Casfen, Gripirinal-Portugal), codeine, caffeine and ascorbic acid (Antigrippine-Portugal), caffeine and thiamine (Vicalmon-Portugal), calcium lactate gluconate (Ascalcin®-Poland), ascorbic acid and calcium lactate gluconate (Polopiryna C Plus, Ascalcin® Plus-Poland), boric acid and zinc peroxide (Cremoldermina (Nho Gorduroso)-Portugal), salicylic acid, camphor, menthol and ammonium salicylate (Radian B Pain Relief Spray-UK, Topical Products for Joint BV Muscular Pain-Malta), aluminum hydroxide and magnesium hydroxide (Ponotex “Adelco”-Greece, Ascriptin A/D-Syria) etylsalitsylamid and caffeine (Etopiryna®, Etomar, FluControl Symptom-Poland) difenidraminu hydrochloride and caffeine (Gripin-Syria) dekstropoksifenu napsilatom and caffeine (Pamoxene, Sedaforte-Syria) izosorbitom mononitrate (Ismorin, ISO A, Isoloprin, Monosprin, Nitren, Solosprin, Vasoprin-India) izosorbitom dinitrate (Asmod-India).

In the market of the Russian Federation is presented ASA in combination with nitroglycerin (Spaskard) in the medicine cabinet in the emergency self-help heart attack as a set of tablets and capsules.

The research can provide active pharmaceutical ingredients, combined with ASA in one dosage form and learn from the experience of countries analyzed ASA combination with other substances. This will allow to study the advisability of expanding the domestic market with new combinations of ASA [58].

3.3 Characteristics of the Demand for Acetylsalicylic Acid Combined Drugs

As a result of processing questionnaires found that 97.5% of respondents pharmacy pill managing demand. Most pharmacies in tablets of ASA bought a month in the amount of 50 or more packages—62.5%. To make sales in 37.5% of analyzed pharmacies bought more than 20 tablets of ASA packages month. Elderly 3 times more likely to buy drugs with ASA compared with adults. Buying pills ASK always carried out without a doctor's prescription.

Combination pills ASA also in demand among consumers, but 12.5% of respondents noted lower its intensity. In 75% of surveyed pharmacies sold more than a month 10-15 combined preparations ASA, 12.5%—5 packages and 12.5%—less than 5 packages. 36 skilled specialists (90% of respondents) believe

appropriate to combine with other substances ASA (vitamin C, caffeine, acetaminophen, magnesium hydroxide).

When the patient medication recommendations 62.5% of pharmacists into account the severity of the disease, 25%—the country of manufacture, and 12.5%—the price of the drug. 95% of respondents believe that it is necessary to take ASA for the prevention of heart attack, but noted only two pharmacists sometimes be necessary. When selecting preparativ ASA by countries producing 55% of respondents prefer Germany, the other 45%—Poland. On possible ulcerogenic effect of combination therapies ASA reported sick all respondents, with 87.5% of course give a full response, and 12.5% increase in profit does not specify this information.

Combinations comprising ASA that are most in demand were determined using the method of a priori ranking. The results of questionnaire show that one place the demand is ASA tablet (mono-drugs) 500 mg; 2 place—tsitramon (ASA 240 mg + 180 mg paracetamol + caffeine 30 mg); 3 place—Askofen (ASA 300 mg + 100 mg paracetamol + caffeine 50 mg); 4th place—Cardiomagnyl (ASC + magnesium hydroxide); 5 place—Kopatsyl (ASA 300 mg + 100 mg paracetamol + caffeine 50 mg); 6 place—Upsaryn UPSA vit.S (ASC + ascorbic acid); 7 place—Alka-Seltzer (ASC + citric acid + sodium bicarbonate); 8th—Alka-Prim (ASC + aminoacetic acid); 9 place—Antyhrypin (ASC + ascorbic acid + sodium rutin + metamizol + calcium gluconate + diphenhydramine); 10 place—Kordynorm plus (ASK + bisoprolol fumarate); 11 place—Ahrenoks (ASA + dipyridamole).

Past studies show differences in supply and demand combined drugs ASA, which requires a reasonable choice of rational drug for drug therapy.

3.4 Pharmacoeconomic Analysis of Acetylsalicylic Acid Combined Drugs

In the next step of the research was grounded feasibility of using combination therapies ASA.

Konturek P. C., Kania J., Hahn E. G., Konturek J. W. (2012) concluded that vitamin C compared to ASA induces less damage to gastric mucosa. Zhao L.-M., Han F. C., Qiu F., Zhang G.-F., Guo S. B. (2004) found that investigated effervescent tablets of aspirin with vitamin C were bioequivalence [59]. This allowed us to use pharmacoeconomic method of minimizing costs. The cost of a single dose Upsarin UPSA with vitamin C table. spike. tuba in box number 10 BMS (France) are 3.80 UAH, Upsarin UPSA with vitamin C table. spike. tuba in box number 20 BMS (France)-1.60 UAH, Aspirin® C table. spike. number 10 Bayer Consumer Care (Switzerland)-3.66 UAH, Asprovit C table. spike. pencil case number 10 Vitale-XD (Estonia)-2.75 UAH, Asprovit C table. spike. strip number 10 Vitale-XD (Estonia)-2.61 UAH. So, from the standpoint of pharmacoeconomic best use Upsarin UPSA with vitamin C table. spike. tuba in box number 20 BMS (France).

Based on twenty studies until August 2014 that included 7,238 participants, established to improve pain relief nonsteroidal anti-inflammatory drugs in combination with caffeine. In the study included several types of pain: headache, toothache after, postoperative pain after childbirth, and menstrual pain period [60].

The Table 1 shows that among combined drugs of ASA with acetaminophen and caffeine at least cost for treatment (6.02 UAH) Requires tsitramon tablets number 6 PJSC “Monpfarm” Ukraine, which is appropriate to recommend to streamline pharmacotherapy.

Diener HC, Pfaffenrath V., Pageler L., Peil H., Aicher B. (2005) in a multicenter, randomized, double-blind, placebo-controlled, parallel-group study found that the fixed combination of ASA with acetaminophen and caffeine is more effective for headache treatment (73% of patients do not feel pain after 30 minutes) than placebo, individual substances and dual combination (66%) [61-64]. Cost-efficiency ratio for Citramon tabl. strip. Number 6 “Monpfarm”

Table 1 Results of calculation of treatment costs for drugs of acetylsalicylic acid in combination with paracetamol and caffeine.

Name of the drug	Pharmaceutical form	Producer	Price package, UAH	The cost of treatment, UAH
Farmadol®	Tablets number 10	JSC "Farmak", Ukraine	5.53	7.70
Citramon-Darnitsa	Tablets number 6	PJSC "Pharmaceutical firm" Darnitsa Ukraine	5.18	8.60
Citramon	Tablets number 6	JSC "Monfarm" Ukraine	2.59	6.02
Citramon Forte	Tablets number 6	PJSC "Lubnyfarm" Ukraine	5.78	9.60
Askofen-Darnitsa	Tablets number 10	PJSC "Pharmaceutical firm" Darnitsa Ukraine	4.64	9.20
Kopacyl®	Tablets number 6	PJSC "Kievmedpreparat" Ukraine	2.95	6.86

Ukraine is $CER = 0.49/0.73 = 0.67$ and for Aspirin tabl. 0.5 g blister number 10 "Monpharm" Ukraine in combination with Paracetamol tabl. 200 mg strip number 10 "Lugansk CPP" Ukraine $CER = 0.46/0.66 = 0.70$. Calculations prove feasibility of using a fixed combination of ASA with acetaminophen and caffeine.

Based on 29 studies involving 23,019 participants Els LLM De Schryver, Ale Algra, Jan van Gijn (2007) compared the effect of the combination of aspirin and dipyridamole on the occurrence of cardiovascular events (stroke, heart attack and death from cardiovascular disease) within 6 months treatment, had the advantage over aspirin (0.99 vs. 0.83) [65, 66]. The cost per unit utility for Agrenox® caps. with modyf. release 200 mg/25 mg number 60 in the bottle Boehringer Ingelheim Pharma GmbH & Co. KG (Germany) was $CUR = 8407.08/0.99 = 8492$ and for Cardiomagnyl table. film-coated shell 75 mg number 100 Nycomed Austria (Austria) $CUR = 116.59/0.83 = 140.47$ testify advisability of including a regimen of ASA at a dose of 75 mg.

These reviews 28,165 people in two studies Alessandro Squizzato, Tymen Keller, Erica Romualdi, Saskia Middeldorp (2011) show that the use of clopidogrel and aspirin is associated with a reduced risk of cardiovascular events (0.87, 95% CI 0.81 to 0.94; $P < 0.01$) and an increased risk of bleeding (1.34, 95% CI 1.14 to 1.57; $P < 0.01$), compared with aspirin [67]. Calculation of cost-utility ratio for Aspigrel caps. numero 100 Mili Healthcare (UK) $CUR = 835.72/0.87 = 960.60$ proves that clopidogrel plus aspirin has a clear positive benefits of risk-benefit in people at high

risk of cardiovascular events (multiple atherothrombotic risk factors) or in people with established cardiovascular disease (coronary heart disease, cerebral or peripheral arterial disease), but not associated with acute coronary syndrome. Therefore, the combination of ASA with clopidogrel should not be used regularly to prevent cardiovascular disease.

Jing Li, Qing Zhang, Mingming Zhang, Matthias Egger (2007) find that magnesium treatment may reduce the incidence of ventricular fibrillation, ventricular tachycardia, severe arrhythmias that require treatment, but it may increase the incidence of profound hypotension, bradycardia; it is unlikely that magnesium reduces mortality when used at high doses (≥ 75 mmol) [51]. Therefore, given the presence of a number of effective treatments for acute myocardial infarction, it would be better to ensure their use, rather than continue to use magnesium for which there was insufficient evidence of effectiveness.

These Duplyakova D.V., Glukhov V.L., Vozhdyyevoyi Z.I., Golovin H.A. (2006) show that antihypertensive effects of beta-blockers did not neutralize the rheological properties of blood under the influence of aspirin. We conducted a comparative analysis of the costs for the treatment of ASA combination therapy with bisoprolol and mono-drugs. Costs for a 2-week course of therapy made Cordynorm® Plus caps. 10 mg + 75 mg numero 30 Actavis Group (Iceland) account for 42.47 UAH, and the combination of Bisoprolol-Astrafarm table. 10 mg blister number 30 Astrafarm (Ukraine) from blood clots ASA 75 mg tabl. film-coated shell solu-quick. 75

Table 2 Summary of the analysis of State Forms of drugs Ukraine.

Year	Combination	Drug
2009	ASA + ascorbic acid	II. Aspiryn® C, C Asprovit
	Dipyridamole + ASA	II. Agrenox®
	ASA + magnesium hydroxide	II. Cardiomagnyl
2010	ASA + ascorbic acid	II. Aspiryn® C, C Asprovit
	Dipyridamole + ASA	II. Agrenox®
	ASA + magnesium hydroxide	II. Cardiomagnyl
2011	ASA + ascorbic acid	II. Aspiryn® C Asprovit C, UPSARYN UPSA with vitamin C
	Dipyridamole + ASA	II. Agrenox®
	ASA + magnesium hydroxide	I. Cormagnil 75, Cormagnil150
2012	ASA + ascorbic acid	II. Aspiryn® C Asprovit C, UPSARYN UPSA with vitamin C
	Dipyridamole + ASA	II. Agrenox®
	ASA + magnesium hydroxide	II. Cardiomagnyl
2013	ASA + ascorbic acid	II. Aspiryn® C Asprovit C, UPSARYN UPSA with vitamin C
	Dipyridamole + ASA	II. Agrenox®
	ASA + magnesium hydroxide	II. Cardiomagnyl, Cardiomagnyl Forte
2014	ASA + ascorbic acid	II. Aspiryn® C Asprovit C, UPSARYN UPSA with vitamin C
	Dipyridamole + ASA	II. Agrenox®
	ASA + magnesium hydroxide	II. Cardiomagnyl, Cardiomagnyl Forte

mg number 30 Valeant Pharmaceuticals (Ukraine) 28.42 UAH. The cost-minimizing analysis established unreasonableness use of combined drugs with ASA bisoprolol.

Past pharmacoeconomic studies allow rationality to justify the use of combined drugs ASA [68].

3.5 The Comparative Characteristic of Government Recommendations for Rational Appointments of Acetylsalicylic Acid combined Drugs

On the basis of six government-issued forms of drugs Ukraine (2009-2014 years) [69-74] was found that the combination of drugs based on ASA recommend the use of ascorbic acid, dipyridamole or magnesium hydroxide. The IMP relate primarily to group II, which contains only a few drugs registered in Ukraine that are repeated from year to year. Summary of the analysis of State Forms of drugs are given in the Table 2.

This shows the incorporation of evidence-based medicine reliable data on their use in the preparation of Drugs Form State of Ukraine.

Formulary article the only mono-drugs, as they are a priority for inclusion in the form. Some of the standard

combination of ASA (combination of paracetamol and caffeine) are not in the Form, which can lead to polypragmasy, reducing the effectiveness and safety of treatment [75].

4. Conclusions

To optimize the State Form Drugs in improving health system in Ukraine can be useful pharmacoeconomic analysis of combination therapies with the current official system. Note the combination of ASA with statins, esomeprazole, izosorbitom.

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