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COMPARATIVE ANALYSIS OF CONSUMER CHARACTERISTICS OF VALSARTAN-CONTAINING PHARMACEUTICAL PRODUCTS IN TERMS OF ASYMMETRIC INFORMATION

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Abstract

The aim of the article was comparative analysis of Instructions for Use of valsartan-containing drug combinations in terms of asymmetric information.

Research materials: data from the State Register of Medicines (SRM) of Ukraine as of September 1, 2019, in particular IFUs of valsartan TMs.

Content analysis, as well as comparative, logical, contextual, and qualitative analysis methods, were used in the research. Based on the study of seven valsartan brands' Instructions for Use, we found the presence of discrepancies in some sections of the texts studied. The results confirm the asymmetric information on the pharmacological identity of analog drugs, as well as the need to take into account the communicative discrepancies in analogs' Instructions for Use to ensure the safe administration of medicines and reduce medication-related problems.

The analysis allows us to conclude that the information provided by the manufacturers in the instructions for use is not always complete. To ensure the reliable and safe administration of the medicines studied, health care professionals should not forget about the quantity, quality and sometimes the side-effects of the the auxilliary substances used.

Keywords: *Valsartan*[1], *drug combinations*[2], *Hypertension*[3], *asymmetric information*[4]

Introduction

More and more medicines are becoming available to patients these days, so consumers will need more high-quality information about the medication they can buy to provide a completely informed decision on medication use.

According to the order of the Ministry of Health of Ukraine №360 of July 19, 2005 No. 360, in the case of patients contacting with a doctor's prescription with the international non-proprietary name (INN) of the drug indicated the pharmacist must offer the trade names of the prescribed medicine and their price categories [1]. The disease is known to be treated by the active pharmaceutical ingredient (API), which the drug contains rather than the trademark (TM) indicated on the package. Drugs with the same API have the same therapeutic effect [2].

These days, the pharmaceutical market is saturated with generic drugs. A wide range of drugs with the same active ingredient makes the problem of interchangeability important. Physicians and pharmacists should consider that drugs with the same international non-proprietary name (INN) and presented in the same dosage form may have different consumer characteristics [3].

Officially approved information on the medical use of drugs that accompanies a finished drug is the instruction for use (IFU) [4]. However, the presence of many trademarks (TM) of medicines with the same international non-proprietary name on the Ukrainian pharmaceutical market can lead to communicative discrepancies in IFUs [5].

The patient, who has no pharmaceutical knowledge about the efficacy of drugs, and the width and depth of their assortment, cannot assimilate a large amount of information that comes from a medical or pharmaceutical professional or an IFU and choose the best medicines required.

Nowadays, for the treatment of hypertension in patients whose blood pressure is not adequately regulated by monotherapy, angiotensin II receptor blockers (ARBs) and diuretics combinations are in high demand in the pharmaceutical market of Ukraine. Valsartan-containing drug combinations are one of the representatives of the group.

In July 2018, the European Medicines Agency (EMA) found contamination with an impurity, a potentially carcinogenic compound N-nitrosodimethylamine (NDMA), in valsartan products manufactured by Zhejiang Huahai Pharmaceutical Co., Ltd. (China), which has supplied its products to pharmaceutical companies around the world. Thus, in July 2018, in accordance with the EMA decision, the State Service of Ukraine on Medicines and Drugs Control began to take actions to recall valsartan drugs of this manufacturer from the Ukrainian market [6].

Our study aimed to compare the texts of valsartan-containing drug combinations IFUs in terms of asymmetric information. Asymmetric information, also known as "information failure," occurs when the pharmacist possesses more knowledge of the specific properties of a medication than the consumer (patient).

Methods

The object of the study was IFUs of valsartan-containing drug combinations, a series of which did not fall under the ban on circulation. Seven IFU texts of TM of Valsartan combinations on INN in tablets of 80 mg included in the State register of medicines of Ukraine as of 01.09.2019 (http://www.drlz.kiev.ua/) were investigated [7]. The analysis of IFUs of the following TMs was carried out: Valsakor H (Krka d.d., Novo Mesto, Slovenia), Vazar H (Actavis Ltd, Malta; Balkanpharma-Dupnitsa JSC, Bulgaria), Vanatex Combi (Pharmaceutical plant Polpharma SA, Poland), Corsar H (PJSC Farmak, Ukraine), Sakord H (Balkanpharma - Dupnitsa AD, Bulgaria), Tiara Duo (PJSC Pharmaceutical firm Darnitsa, Ukraine), Diocor 80 (LLC Pharma Start, Ukraine) [8].

The choice of IFU as the object of study is justified by the following: the IFU text as a document, on the one hand, serves as a tool of indirect communication between a doctor and a patient and, on the other hand, helps to achieve the main goal of the doctor and pharmacist, i.e. to successfully inform the consumer/patient about the correct use of the medicine he needs. The study showed that patients who read IFUs were more likely to follow them. Although doctors and pharmacists are desirable sources of information, they, unfortunately, do not always provide their patients/consumers with optimal knowledge.

Moreover, oral information is easy to misunderstand or forget; therefore, they supply pharmaceuticals with a paper IFU. The researchers also found that problems with reading and understanding IFUs in patients with myocardial infarction could result in medication misuse and contribute to reduced patients' willingness to follow the doctor's recommendations, their conscientiousness, and their propensity to treatment.

Thus, an adequate perception and understanding of the text of instructions for use by consumers without special (medical/pharmaceutical) training are of great importance.

Content analysis, as well as comparative, logical, contextual, and qualitative analysis methods, were used in the research.

Results

A comparative textual analysis of IFUs included the following consumer characteristics: composition, indications for administration, contraindications, interaction with other drugs, side effects, overdose, conditions for dispensing a medicine. All the drugs studied are the prescription ones and have antihypertensive and diuretic effects.

The study of the composition of TM drugs showed that the APIs of the analyzed drugs were the same, the first substance was valsartan, and the second one was hydrochlorothiazide. In vivo bioequivalence studies proved the interchangeability for Vazar H and Vanatex Combi only (B1) [9].

According to the researchers, the statement about the pharmacological identity of drug analogs of different TMs without bioequivalence data contains asymmetric information and can cause medication-related problems[10].

A comparative textual analysis of IFU allowed for revealing several differences in them. Medicines studied are different in name and their excipients amount. Excipients do not just provide the technological possibility of obtaining certain medicines in a particular dosage form but also determine or regulate their stability. Pharmaceutical excipients (fillers) "are not intended to affect physiological processes and should not have a direct biological or therapeutic effect." They are added to medicines for stability and effectiveness over time, to improve absorption, taste or appearance, etc. A total of 19 excipients from 8 to 14 in one drug are in the TM combination studied (Table 1).

The most commonly used excipients are magnesium stearate, colloidal anhydrous silica, titanium dioxide (E 171) and macrogol (all TMs); microcrystalline cellulose, croscarmellose sodium, and iron oxide red (E 172) - in 6 TMs; lactose monohydrate, polyvinyl alcohol, and iron oxide yellow (E 172) - in 5 TMs. Excipients affect drug stability and shelf life. In particular, according to IFU, the shelf life of one TM Valsartan combination (Tiara Duo) is two years, of the other four (Vanatex Combi, Corsar H, Sacord H and Diocor 80) - three years, and that of Vazar H and Valsacor H - four and five years, respectively.

The further results revealed some differences in the indications and contraindications for different TM Valsartan combinations.

Essential hypertension (EHT) is the indication for the administration of four TMs, while HTN is the indication for the use of three TMs studied (Table 2). HTN frequency does not exceed 10% of all cases of hypertension [11].

Furthermore, the contraindications to TM Valsartan combinations were studied. Comparative analysis of contraindications found eight contraindications in all IFUs studied (Table 3). Five of them are common to all, namely: hypersensitivity to the active ingredient and/or excipients as well as to sulfonamide derivatives; severe liver dysfunction, cholestasis or liver cirrhosis; anuria, severe renal impairment (creatinine clearance <30 ml/min); refractory hypokalemia, hyponatremia, hypercalcemia, secondary hyperuricemia.

Some information is absent in several IFUs while it is available in others. For example, only the TM Vazar H IFU includes hypersensitivity to peanuts or soy as a contraindication.

An important contraindication in six TM Valsartan combinations is the concomitant use with aliskiren. Corsair H is the only TM where aliskiren is not listed even in the section Drug Interaction.

Comparative assessment of drug interaction found that IFUs present the drug options, both for the combination of active substances and separately for valsartan and hydrochlorothiazide.

All drugs are combinations, so IFUs have a section Interactions associated with both valsartan and hydrochlorothiazide. In this section, all TMs indicate lithium as not recommended for concomitant use. IFUs of all TMs include cautions for the concomitant use of pressor amines, non-steroidal anti-inflammatory drugs (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid> 3 g / day, and non-selective NSAIDs, and other antihypertensive drugs.

In the section Interactions related to valsartan of all IFUs, drugs that can increase blood potassium levels are specified as not recommended for concomitant use. However, this section, except that of Corsair H IFU, specifies transporters. Separately, all instructions provide information that drug-drug interaction studies of valsartan have not shown clinically significant interactions between valsartan and any of the following drugs: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide.

In the section Interactions related to hydrochlorothiazide almost all TMs provide the list of groups of drugs that require caution when used concomitantly. Vazar H, Sacord H, and Tiara Duo have cautions when used concomitantly with drugs that can induce ventricular tachycardia such as pirouette, but indicated the condition as polymorphic ventricular tachycardia ("torsades de pointes"). Six medication IFUs report about the dual blockade of the renin-angiotensin-aldosterone system(RAAS) by ARBs, ACE inhibitors, or aliskiren, as requiring precaution, medical supervision, or not recommended at all. Corsar H is the only that does not inform about the caution of concomitant use of drugs that affect serum sodium and the dual blockade of RAAS, whereas the other TMs do.

The studies of the section Use during pregnancy and lactation (Table 4) found five TM valsartan combinations to be strictly contraindicated during pregnancy and breastfeeding, Vazar H "is not used at that time" and Tiara Duo "should not be used". IFUs of all TMs include a special condition of use: if pregnancy is confirmed during the treatment with this drug its use should be stopped immediately and it should be replaced with other drugs approved for use by pregnant women.

Regarding the use during breastfeeding, the IFUs state that if treatment with Valsacor H, Corsar H, Sacord H, Tiara Duo, and Diocor 80 is required, breastfeeding should be discontinued. In the case of prescribing Vazar H and Vanatex Combi, breastfeeding is not recommended. When used in pediatrics, six IFUs do not recommend to use TM Valsartan combinations and Diocor 80 should not be used.

The next step was to compare IFU sections Overdose and Adverse reactions. The main sign of overdosage of the pharmaceutical ingredient (API) - valsartan - may be hypotension with dizziness. Treatment depends on the time elapsed after taking the drug and the severity of symptoms; stabilization of hemodynamics is the most important thing. Valsartan is not eliminated by dialysis due to significant binding to plasma proteins.

In the course of the studies, we analyzed the number of adverse reactions (ADR) specified in the IFUs. When used, all the drugs studied can cause side effects. Diocor 80 IFU lists the largest number of adverse reactions, while Vanatex Combi IFU lists the fewest ADRs. The analyzed IFU texts contain 13 groups of ADRs on average, ranging from 11 to 14 (Fig.1). The number of possible adverse clinical manifestations is, on average, 82 ranging from 22 to 107.

Discussion

To sum up, it should be noted that the results of the study indicate the presence of asymmetric information in the texts of IFUs on the pharmacological identity of drug analogues.

Thus, medical and pharmaceutical workers should take into account the problem of the communicative discrepancy in IFUs of drug analogues to ensure the reliable and safe administration and use of drugs by patients.

Differences in consumer characteristics of identical in composition medicines indicate the presence of two main factors of influence: the peculiarities of the technological process used by manufacturers and the different amounts of excipients.

Conclusions

Comparative assessment of the consumer properties of the drugs in the form of tablets revealed some differences in indications for use, as well as differences in qualitative and quantitative composition of excipients, contraindications, side effects, descriptions of interactions with other drugs, and shelf life. The information provided by pharmaceutical manufacturers in Instructions for Use is not always complete.

Thus, to ensure the reliable and safe administration of the drugs studied, health professionals should not forget about the differences in their consumer properties and individual approach to use by patients.

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Table 1. list of Excipients of TM Valsartan combination

Composition of excipients		TM Valsartan combination							Total
		Valsakor H	Vazar H	Vanatex Combi	Corsar H	Sakord H	Tiara Duo	Diocor 80	
1.	Lactose monohydrate	+	+	+	+	+	–	–	5
2.	Microcrystalline cellulose	+	+	–	+	+	+	+	6
3.	Magnesium stearate	+	+	+	+	+	+	+	7
4.	Croscarmellose sodium	+	+	+	+	+	–	+	6
5.	Sodium lauryl sulfate	–	–	–	–	–	–	+	1
6.	Colloidal anhydrous silica	+	+	+	+	+	+	+	7
7.	Cornstarch	–	–	–	–	–	–	+	1
8.	Potato starch	–	–	–	–	–	–	+	1
9.	Hypromellose	+	–	+	–	–	–	–	2
10.	Povidone	+	+	–	+	+	–	–	4
11.	Crosspovidone	–	–	–	–	–	+	–	1
12.	Polyvinyl alcohol	–	+	–	+	+	+	+	5
13.	Titanium dioxide (E 171)	+	+	+	+	+	+	+	7
14.	Macrogol	+	+	+	+	+	+	+	7
15.	Iron oxide yellow (E 172)	+	+	–	+	+	+	–	5
16.	Iron oxide red (E 172)	+	+	+	+	+	+	–	6
17.	Iron oxide black (E 172)	–	–	–	+	+	–	–	2
18.	Lecithin	–	+	–	+	+	+	–	4
19.	Talk	–	+	–	+	+	–	+	4
Total		11	13	8	14	14	10	11	81
Shelf life, years		5	4	3	3	3	2	3	x

Table 2. indications to TM Valsartan combinations

Indicators	TM Valsartan combinations						
	Valsakor H	Vazar H	Vanatex Combi	Corsar H	Sakord H	Tiara Duo	Diocor 80
Essential hypertension	–	+	–	–	+	+	+
Hypertension	+	–	+	+	–	–	–

Table 3. contraindications to TM Valsartan combinations

Indicators	TM Valsartan combinations						
	Valsakor H	Vazar H	Vanatex Combi	Corsar H	Sakord H	Tiara Duo	Diocor 80
All TMs							
1. Hypersensitivity to the active ingredient and/or excipients							
2. Severe liver dysfunction, liver cirrhosis or cholestasis							
3. Anuria, severe renal impairment (creatinine clearance <30 ml/min)							
4. Refractory hypokalemia, hyponatremia, hypercalcemia, secondary hyperuricemia							
5. hypersensitivity to sulfonamide derivatives							
6. Pregnant women and women planning to become pregnant	+	+	+	–	+	+	+
7. Hypersensitivity to peanuts or soy	–	+	–	–	–	–	–
8. Concomitant use of angiotensin II receptor blockers (ARBs), including valsartan, or angiotensin-converting-enzyme inhibitors (ACE inhibitors) with aliskiren in patients with diabetes mellitus or renal failure.	+	+	+	–	+	+	+

Table 4. use of TM Valsartan combinations during pregnancy and lactation and in children

TM Valsartan combinations	Administration features		
	during pregnancy	during the period of breastfeeding	in children
Valsakor H	contraindicated	breastfeeding should be stopped	not recommended
Vazar H	not to use	breastfeeding is not recommended	
Vanatex Combi	contraindicated		
Corsar H		breastfeeding should be stopped	
Sakord H			
Tiara Duo	should not be used		
Diocor 80	contraindicated		should not be used

Figure 1. number of adverse reactions TM Valsartan combinations