Recommended by Doctor of Pharmacy, professor N.P.Polovko

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THE BIOPHARMACEUTICAL STUDIES OF VALAVIR FILM-COATED TABLETS, 0.5 g

S.M.Gureyeva, A.M.Goy, Yu.A.Kondratova, O.H.Oksamytna

Farmak JSC

Key words: biopharmaceutical studies; bioavailability; bioequivalence; test drug product; reference drug product; Valavir 0.5 g film-coated tablets

The biopharmaceutical studies of Valavir film-coated tablets, 0.5 g, with valaciclovir hydrochloride have been substantiated in the article. The biopharmaceutical studies have been conducted in vitro; the dissolution profiles of Valavir film-coated tablets, 0.5 g, and the reference drug Valtrex (film-coated tablets, 500 mg, manufactured by GlaxoSmithKline Pharmaceuticals S.A., Poland) have been compared by the method for Dissolution Kinetics. The results of the experimental study in vivo, namely the value of C_{max}, AUC_{0-t} and other values confirm that Valavir film-coated tablets, 0.5 g, manufactured by Farmak JSC is bioequivalent to the reference drug Valtrex film-coated tablets, 500 mg (GlaxoSmithKline Pharmaceuticals S.A., Poland).

Bioequivalence and bioavailability studies of drugs allow to conduct a rational, selective, comprehensive and efficient pharmacotherapy. Comparative biopharmaceutical studies (experiments *in vitro* / *in vivo*) complement the scientific basis of evidence-based medicine.

Concerning the pharmaceutical technology of solid dosage forms the biopharmaceutical studies confirm the expedience of selecting excipients and film coating to improve qualitative organoleptic characteristics (appearance, corrected taste, moisture resistance) and pharmacotechnological parameters for convenient use and storage of a drug [1, 3, 5].

The bioequivalence study is a knowledge-based process requiring specific clinical trials and testing of multiple samples of drugs by highly sensitive methods (chromatography-mass spectrometry, tandem mass spectrometry, etc.) with the high cost of studies. Therefore, pre-studies *in vitro* are usually conducted. The conformity of the kinetics of the active substance release of the drugs developed with original drugs may, to a certain degree of probability, predict similar kinetics in the experiment *in vivo*.

Valaciclovir is a new antiviral drug (ester L-valine hydrochloric salt of acyclovir), which is rapidly and almost completely converted to acyclovir in the human body under the action of valaciclovir hydrolase enzyme. Compared to acyclovir [4], the benefits of valaciclovir include better solubility and bioavailability [6].

The half-life of acyclovir after administration of valaciclovir is about 3 hours. The high concentration in the blood plasma created by higher bioavailability of valaciclovir allows reducing the dosage regimen by 1.5 times, and it significantly improves efficiency and safety of the drug.

The aim of this study was to conduct the biopharmaceutical studies of Valavir film-coated tablets, 0.5 g, with valaciclovir hydrochloride.

Materials and Methods

The biopharmaceutical studies were conducted *in vitro*; the dissolution profiles of Valavir film-coated tablets, 0.5 g, and the reference drug Valtrex (film-coated tablets, 500 mg, manufactured by GlaxoSmithKline Pharmaceuticals S.A., Poland) were compared by the method for Dissolution Kinetics developed by us. Dissolution profiles were studied in two media with pH 1.2 and 4.5 as recommended by the State Pharmacopeia of Ukraine (SPhU) [2]. Validity of the given method was proven by the results of the previous experimental studies; the range of the method was determined for the media used and the criteria for comparison of the validation data obtained were substantiated [4]. The results of the study are given in Tables 1-4 below. Dissolution profiles are presented in Fig. 1 and 2.

Comparative pharmacokinetic studies to assess bioequivalence of Valavir film-coated tablets, 0.5 g, and Valtrex (film-coated tablets, 500 mg, manufactured by GlaxoSmithKline Pharmaceuticals S.A., Poland) were conducted in healthy volunteers using the method based on 90% confidence intervals for the relationship of logarithmically transformed mean values C_{max} and AUC_{0-t} of the test and reference drugs, which should be within the range of 0.8000÷1.2500 (80.00÷125.00%). The open-label, comparative, randomized, two-period, two-way, crossover study was conducted with administration of a single dose of 500 mg of Valaciclovir hydrochloride of the test and reference drugs in healthy volunteers under fasting condition.

There were 18 healthy male and female volunteers aged 18 to 50 years old who met all the requirements of the inclusion/non-inclusion criteria in the study. Bioequivalence of Valavir film-coated tablets, 0.5 g, was assessed on the basis of statistical analysis of the pharmacokinetic parameters of the study.

For the quantitative determination of the content of valaciclovir in the model media *in vitro* and the biologi-

Table 1

Dissolution profiles of Valavir film-coated tablets, 0.5 g, in the model medium (pH 1.2, 900 mL, 75 rpm)

Batch No. 71010	Test Drug				
Tablet No.	Dissolution Time, min				
	0	10	15	20	30
Tablet 1	0	82.7	94.1	98.7	101.1
Tablet 2	0	81.9	93.3	98.2	101.0
Tablet 3	0	75.8	93.7	100.2	101.8
Tablet 4	0	73.7	92.3	99.1	101.5
Tablet 5	0	87.5	96.2	100.2	102.6
Tablet 6	0	82.4	95.8	99.3	100.4
Tablet 7	0	84.5	95.9	99.6	100.6
Tablet 8	0	83.2	95.6	99.0	101.0
Tablet 9	0	81.4	96.5	101.3	103.6
Tablet 10	0	88.7	96.0	99.0	100.4
Tablet 11	0	87.9	97.0	101.5	102.5
Tablet 12	0	87.1	98.3	101.7	104.1
Mean		83.1	95.4	99.8	101.7
Standard deviation		4.7	1.7	1.2	1.2

Table 2

Dissolution profiles of Valtrex film-coated tablets, 500 mg, in the model medium (pH 1.2, 900 mL, 75 rpm)

Batch No. PA0514	Reference Drug Product				
Tablet No.	Dissolution Time, min				
	0.	10	15	20	30
Tablet 1	0	73.2	82.8	97.9	109.0
Tablet 2	0	68.0	78.7	93.8	102.1
Tablet 3	0	72.4	80.6	92.9	110.1
Tablet 4	0	76.1	85.2	97.6	108.8
Tablet 5	0	70.0	79.8	90.6	108.1
Tablet 6	0	73.4	82.0	95.0	109.8
Tablet 7	0	78.3	87.2	98.5	108.9
Tablet 8	0	72.7	81.3	91.4	106.5
Tablet 9	0	83.2	90.4	101.8	105.1
Tablet 10	0	79.2	84.9	96.8	105.8
Tablet 11	0	72.9	78.5	94.6	109.0
Tablet 12	0	83.0	89.4	99.5	105.6
Mean	0	75.2	83.4	95.9	107.4
Standard deviation		4.8	4.0	3.4	2.4

The similarity factor f2 = 54.79.

cal media *in vivo* liquid chromatography with a spectrophotometric detector was used as the most selective method among available methods since pharmacokinetics of placebo of the original drug was unknown.

Mathematical calculation and statistical analysis of the pharmacokinetic parameters were performed using WinNonLin v. 5.2 with IVIVC Tool Kit software (Pharsight Corp., USA).

Results and Discussion

Based on the results of the biopharmaceutical studies *in vitro* using the method for Dissolution Kinetics the similarity profiles of Valavir film-coated tablets, 0.5 g, and Valetrex film-coated tablets, 500 mg (GlaxoSmith-Kline Pharmaceuticals S.A., Poland), were determined. When releasing into the model medium with pH 1.2 (75 rpm), the similarity factor is 54.79; when releasing into the model medium with pH 4.5 (75 rpm), the similarity factor is 57.15. It allows to predict similar bioavailability of the test and reference drugs.

After administration of the test drug Valavir film-coated tablets, 0.5 g, and the reference drug Valtrex the mean values of the maximum plasma concentration (C_{max}) of acyclovir in volunteers were 256.31 and 2388.36 ng/mg, respectively (Table 5). The mean values of the area under the pharmacokinetic curves from the zero point to the end point of the blood collection (AUC_{0-t}) were 8033.46 ng · h/ml and 8635.82 ng · h/ml for Valavir and Valtrex, respectively.

Fig. 3 presents the curves of the "concentration-time" dependence (the arithmetic mean) for acyclovir in the plasma of volunteers (n = 18) after single-dose administration of Valaciclovir film-coated tablets, 0.5 g, and Valtrex film-coated tablets, 500 mg.

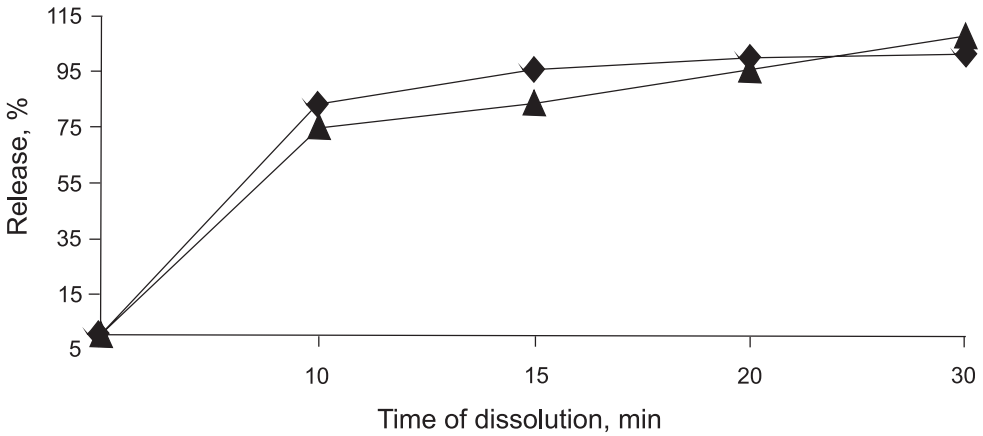

Fig. 1. Dissolution profiles of Valavir film-coated tablets, 500 mg, and Valtrex film-coated tablets, 500 mg, in the buffer solution with pH 1.2.

Table 3

Dissolution profiles of Valavir film-coated tablets, 0.5 g, in the model medium (pH 4.5, 900 ml, 75 rpm)

Batch No. 71010	Test Drug				
Tablet No.	Dissolution Time, min				
	0.	10	15	20	30
Tablet 1	0	34.0	52.0	63.4	78.4
Tablet 2	0	42.1	60.5	72.4	83.9
Tablet 3	0	24.9	38.6	50.8	71.9
Tablet 4	0	42.4	61.0	72.3	86.3
Tablet 5	0	43.1	60.5	73.8	87.0
Tablet 6	0	49.2	64.1	75.0	85.5
Tablet 7	0	41.4	57.9	73.3	84.9
Tablet 8	0	37.5	52.4	67.1	84.8
Tablet 9	0	35.1	49.7	63.1	83.1
Tablet 10	0	44.6	62.7	74.5	87.1
Tablet 11	0	49.0	65.2	76.1	89.4
Tablet 12	0	50.2	63.6	74.8	89.0
Mean	0	41.1	57.4	69.7	84.3
Standard deviation		7.4	7.8	7.4	4.9

Table 4

Dissolution profiles of Valtrex film-coated tablets, 500 mg, in the model medium (pH 4.5, 900 ml, 75 rpm)

Batch No. PA0514	Reference Drug				
Tablet No.	Dissolution Time, min				
	0.	10	15	20	30
Tablet 1	0	36.9	49.5	62.5	77.0
Tablet 2	0	40.1	55.3	65.3	80.0
Tablet 3	0	44.7	56.0	64.7	77.7
Tablet 4	0	36.2	49.8	59.1	76.1
Tablet 5	0	41.3	54.0	62.9	78.8
Tablet 6	0	31.2	40.2	49.9	65.6
Tablet 7	0	37.2	49.7	61.5	77.3
Tablet 8	0	37.9	54.7	63.8	81.6
Tablet 9	0	42.2	55.9	62.9	78.9
Tablet 10	0	36.2	49.3	58.4	75.7
Tablet 11	0	39.2	53.6	61.6	80.0
Tablet 12	0	32.8	43.0	51.0	67.1
Mean	0	38.0	50.9	60.3	76.3
Standard deviation		3.8	5.1	5.0	5.0

The similarity factor f2=57.15.

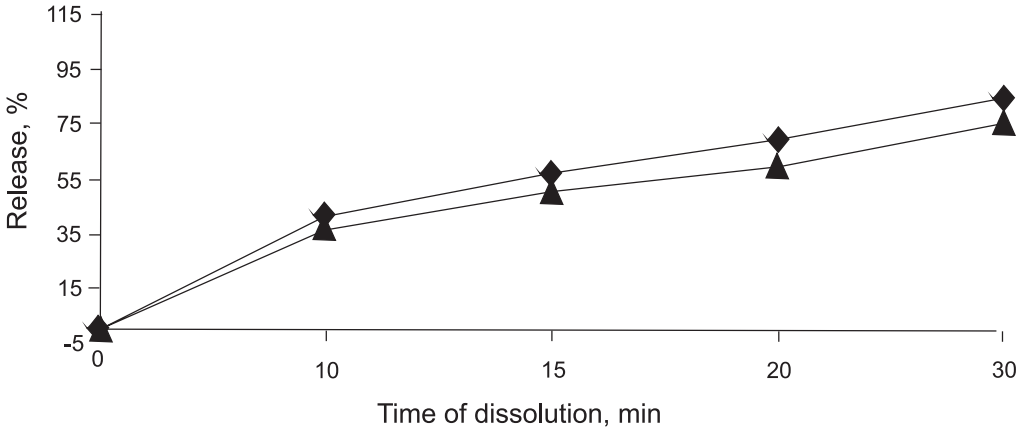

Fig. 2. Dissolution profiles of Valavir film-coated tablets, 500 mg, and Valtrex film-coated tablets, 500 mg, in the buffer solution pH 4.5.

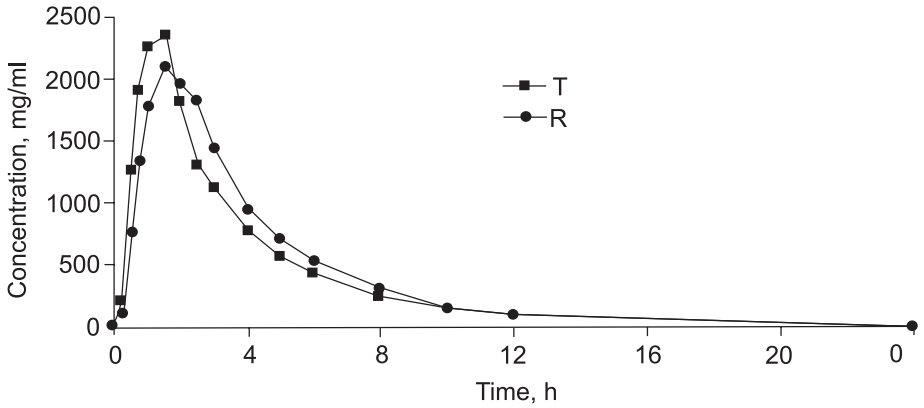

Fig. 3. The curves of the "concentration-time" dependence (the arithmetic mean) for acyclovir in the plasma of healthy volunteers after single-dose administration of the drugs Valavir film-coated tablets, 0.5 g, and Valtrex film-coated tablets, 500 mg.

Table 5

Pharmacokinetic parameters of Valavir film-coated tablets, 0.5 g, and the reference drug Valtrex

Drugs	Pharmacokinetic parameters						
	C_{max}, ng/mL	T_{max}, h	AUC_{0-t}, ng • h/ml	$AUC_{0-\infty}$, ng • h/ml	AUC_{0-t} / $AUC_{0-\infty}$, %	K_{el}, h^{-1}	$t_{1/2}$, h
Valavir film-coated tablets, 0.5 g	2566.31	1.26	8033.46	8371.83	95.98	0.28	2.56
Valtrex film-coated tablets, 500 mg	2388.36	1.79	8635.82	9023.87	95.61	0.29	2.50

The ranges for 90% confidence intervals for the relationship between logarithms of the mean values C_{max} and AUC_{0-t} of the test and reference drugs were 97.29 ÷ 124.04% and 86.32 ÷ 102.58% (disregarding the correction factor, which is equal to 0 in this study, and its ln = 0). The results obtained correspond to the bioequivalence criterion of 80.00-125.00% for C_{max} and AUC_{0-t}.

The results of the experimental study *in vivo*, namely the value of C_{max}, AUC_{0-t} and others confirm that Valavir film-coated tablets, 0.5 g, manufactured by Farmak JSC is bioequivalent to the reference drug Valtrex film-coated tablets, 500 mg, (GlaxoSmithKline Pharmaceuticals S.A., Poland).

CONCLUSIONS

The biopharmaceutical studies conducted confirm that Valavir film-coated tablets, 0.5 g, with valaciclovir hydrochloride manufactured by Farmak JSC is bioequivalent to the reference drug Valtrex film-coated tablets, 500 mg, (GlaxoSmithKline Pharmaceuticals S.A., Poland).

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БІОФАРМАЦЕВТИЧНІ ДОСЛІДЖЕННЯ ПРЕПАРАТУ ВАЛАВІР 0,5 г, ТАБЛЕТКИ, ВКРИТІ ОБОЛОНКОЮ

С.М.Гуреєва, А.М.Гой, Ю.А.Кондратова, О.Г.Оксамитна

Ключові слова: *біофармацевтичні дослідження; біодоступність; біоеквівалентність; досліджуваний препарат; референтний препарат; таблетки Валавір 0,5; вкриті оболонкою*

Обосновані та відображені біофармацевтичні дослідження препарату Валавір з Валацикловіру гідрохлоридом 0,5 г, таблетки, вкриті оболонкою. Проведені біофармацевтичні дослідження in vitro – порівняння профілів розчинення таблеток Валавіру 0,5, вкритих оболонкою, та референтного препарату Вальтрекс (таблетки 500 мг, вкриті оболонкою, «ГлаксоСмітКляйн Ф. С.А.», Польща) методикою «Кінетика розчинення». Результати експериментального дослідження in vivo, а саме значення C_{max}, AUC_{0-t} та ін. підтверджують, що препарат Валавір 0,5 г, таблетки, вкриті оболонкою, виробництва ПАТ «Фармак» є біоеквівалентним референтному препарату Вальтрекс 500 мг, таблетки, вкриті оболонкою («ГлаксоСмітКляйн Ф. С.А.», Польща).

БИОФАРМАЦЕВТИЧЕСКИЕ ИССЛЕДОВАНИЯ ПРЕПАРАТА ВАЛАВИР 0,5 г, ТАБЛЕТКИ, ПОКРЫТЫЕ ОБОЛОЧКОЙ

С.Н.Гуреева, А.М.Гой, Ю.А.Кондратова, Е.Г.Оксамитная

Ключевые слова: *биофармацевтические исследования; биодоступность; биоэквивалентность; исследуемый препарат; референтный препарат; таблетки Валавир 0,5; покрытые оболочкой*

В статье обоснованы и отражены биофармацевтические исследования препарата Валавир с Валацикловира гидрохлоридом 0,5 г, таблетки, покрытые оболочкой. Проведены биофармацевтические исследования in vitro – сравнение профилей растворения таблеток Валавир 0,5, покрытых оболочкой, и референтного препарата Вальтрекс (таблетки 500 мг, покрытые оболочкой, «ГлаксоСмітКляйн Ф. С.А», Польша) по методике «Кинетика растворения». Результаты экспериментального исследования in vivo, а именно значение C_{max}, AUC_{0-t} и др., подтверждают, что препарат Валавир 0,5 г, таблетки, покрытые оболочкой, производства ПАО «Фармак» является биоэквивалентным референтному препарату Вальтрекс 500 мг, таблетки, покрытые оболочкой («ГлаксоСмітКляйн Ф. С.А», Польша).