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

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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 $C_{\text{max}}$, $AUC_{0-t}$, 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 conducted 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 $C_{\text{max}}$ 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-
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                   |

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 $f_2 = 54.79$.

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 Valtrex film-coated tablets, 500 mg (GlaxoSmithKline 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/ml, 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 $\cdot$ h/ml and 8635.82 ng $\cdot$ 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.
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 | Tablet No. | Test Drug | 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 | Tablet No. | Reference Drug | 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 | 66.5 |
| 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 $f_2 = 57.15$. 

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.
The ranges for 90% confidence intervals for the relationship between logarithms of the mean values $C_{\text{max}}$ and $AUC_{0-t}$ of the test and reference drugs were $97.29 \div 124.04\%$ and $86.32 \div 102.58\%$ (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 $C_{\text{max}}$ and $AUC_{0–t}$.

The results of the experimental study in vivo, namely the value of $C_{\text{max}}$, $AUC_{0-t}$ 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).

**Table 5**

| Drugs                               | Pharmacokinetic parameters                                                                 |
|-------------------------------------|-------------------------------------------------------------------------------------------|
|                                     | $C_{\text{max}}$, ng/mL | $T_{\text{max}}$, h | $AUC_{\text{max},0-t}$, ng$\cdot$h/ml | $AUC_{\infty,0-t}$, ng$\cdot$h/ml | $AUC_{0-t}/AUC_{\infty,0-t}$, % | $K_{\text{el}}$, 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          |

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**БИОФАРМАЦЕВТИЧНІ ДОСЛІДЖЕННЯ ПРЕПАРАТУ ВАЛАВІР 0,5 г, ТАБЛЕТКИ, ВКРИТИ ОБОЛОНКОЮ**

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Ключові слова: біофармацевтичні дослідження; біодоступність; біоєквівалентність; досліджуваний препарат; референтний препарат; таблетки Валавір 0,5 г, вкриті оболонкою. Обосновані та відображено біофармацевтичні дослідження препарату Валавір з Валацикловіра гідрохлоридом 0,5 г, таблетки, вкриті оболонкою. Проведені біофармацевтичні дослідження in vitro – порівняння профілів розчинення таблеток Валавіру 0,5, вкритих оболонкою, та референтного препарата Вaltarекс (таблетки 500 мг, вкриті оболонкою, «ГлаксоСмітКляйн Ф. С.А.», Польща) методикою «Кінетика розчинення». Результати експериментального дослідження in vivo, а саме значення $C_{\text{max}}$, $AUC_{\text{max},0-t}$, та ін. підтверджують, що препарат Валавір 0,5 г, таблетки, вкриті оболонкою, виробництва ПАТ «Фармак» є біоєквівалентним референтному препарату Вaltarекс 500 мг, таблетки, вкриті оболонкою («ГлаксоСмітКляйн Ф. С.А.», Польща).

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

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Ключевые слова: биофармацевтические исследования; биодоступность; биоэквивалентность; исследуемый препарат; референтный препарат; таблетки Валавир 0,5 г, покрытые оболочкой. В статье обоснованы и отражены биофармацевтические исследования препарата Валавир с Валацикловиром гидрохлоридом 0,5 г, таблетки, покрытые оболочкой. Проведены биофармацевтические исследования in vitro – сравнение профилей растворения таблеток Валавир 0,5 г, покрытых оболочкой, и референтного препарата Вaltarекс (таблетки 500 мг, покрытые оболочкой, «ГлаксоСмитКляйн Ф. С.А.», Польша) методикой «Кинетика растворения». Результаты экспериментального исследования in vivo, а именно значение $C_{\text{max}}$, $AUC_{\text{max},0-t}$ и др., подтверждают, что препарат Валавир 0,5 г, таблетки, покрытые оболочкой, производства ПАО «Фармак» является биоэквивалентным референтному препарату Вaltarекс 500 мг, таблетки, покрытые оболочкой («ГлаксоСмитКляйн Ф. С.А.», Польша).