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## **PROTEFLAZID<sup>®</sup>: Efficacy and Safety in Urogenital Herpes Virus Infection (Systematic Review)**

**Abstract:** In preclinical studies of antiherpetic drug activity, it was proved that Proteflazid<sup>®</sup> has polypharmacological effects. It blocks DNA polymerase and thymidine kinase in the herpes-infected cells, induces the synthesis of endogenous  $\alpha$ - and  $\gamma$ -interferons, has an antioxidant activity and provides an apoptosis-modulating effect. In clinical practice, the etiopathogenetic drug efficacy of Proteflazid<sup>®</sup> (drops for oral and topical application) is confirmed in the treatment of genital herpes infections, including the mixed infection.

This systematic review, conducted on the basis of 37 clinical trials between 2000 and 2015, involving more than 1,900 patients, proves the safety and therapeutic efficacy of the Proteflazid<sup>®</sup> for the treatment of herpes virus diseases in urogenital tract of both men and women.

**Keywords:** Proteflazid<sup>®</sup>, antiviral activity, herpes virus infection, genital herpes, recurrent herpes, prevention, treatment.

**Actuality.** *Genital herpes (GH)* is one of the most common, clinically and socially significant forms of herpes infection. According to preliminary data, the negotiability to doctors of various specialties (gynecologists, urologists, dermatovenerologist) is not more than 15% of the real disease frequency. The fact that the increased incidence is faster than the growth rate of world population causes alertness [1].

Genital herpes is a disease of reproductive organs caused by herpes simplex virus (Herpes simplex virus, HSV). Now eight most dangerous types of human herpes virus are known, among them two types (HSV-1 and HSV-2) cause GH. In 80% of cases the genital herpes is caused by HSV-2 and only 20% of cases are caused by HSV-1 or mixture of viruses. The first type of virus often causes the first episode of GH. Repeated manifestations of GH are almost always associated with HSV-2. In most cases GH is asymptomatic and persists in the urogenital tract (in males), and in the cervical canal, vagina and urethra (in females). Persons with asymptomatic disease are a reservoir of infection. GH infection occurs mainly through sexual contact. The virus is introduced through the mucous membranes and skin, hereinafter a gradual involvement in the pathological process firstly of vulva, then the vagina, cervix, urethra, and finally, bladder, prostate, and testes in males and bladder, uterus, appendages in females is observed. At this stage in case of pregnancy placenta and fetus become infected. Genital HSV infection during pregnancy is a significant risk for the development of fetus and newborn [2, 3].

The important fact is that chronic, often recurrent HSV infection may trigger the development of autoimmune states (antiphospholipid syndrome, autoimmune thyroiditis, autoimmune vasculitis and others). In addition, during the integration of HSV in the genetic apparatus the neoplastic transformation of cells may be provoked. Thus, HSV is one of the risk factors in uterus and cervix cancer development. Herpes virus infection is a leading cause of spontaneous abortion, premature birth, birth of children with CNS and internal organs pathology.

Tactics of herpes virus infections treatment is aimed primarily at relief of active infection, and its character is determined by the severity and frequency of exacerbations, clinical manifestations of diseases, their complications and the risk of transmission. In this context, the objectives and the direction of the herpes virus infections treatment are to suppress reproduction of an infectious agent during the acute manifestations of congenital or acquired infection (initial episode of the disease or its aggravation - relapse), prevention of latent infections, formation of an adequate immune response with a long-term preservation aiming at blocking of the process of infection reactivation in the foci of persistence, as well as prevention of any kind of transmission to the fetus and the baby vertically, horizontally or in other ways.

In recent years there is both an increase in the incidence of herpes infections and increase in the number of their acyclovir-resistant forms [5]. At the same time,

almost a half of the patients who suffer from herpes virus infection in the first one or two years after the previous acute episode has relapses, and the number of cases with chronic recurrent disease occurs in more than 12% of the infected [1]. According to scientific data, the probability of the formation of herpes virus strains resistant to acyclic nucleosides can be up to 25% of cases [6].

In this regard, as a causal therapy to suppress herpes viruses breeding flavonoids which have a strong antiviral effect are widely used. Thus, the antiviral preparation Proteflazid<sup>®</sup> (drops) (Scientific & Manufacturing Company "Ecopharm" Ltd, Kiev, Ukraine) has been used in our country and abroad since 2002 as a highly effective antiherpetic medication. Its active ingredients include flavonoids derived from wild cereals *Deschampsia caespitosa* L. and *Calamagrostis epigeios* L.

**Objective:** to analyze the theoretical and practical evidence base that confirms the efficacy and safety of Proteflazid<sup>®</sup> (drops) in clinical practice for the treatment of herpes virus infections.

**Materials and Methods:** scientific publications, reports on preclinical and clinical studies, systematic analysis.

**Results and discussion.** In the systematic review the results of preclinical and clinical research studies of Proteflazid<sup>®</sup> (drops) in the scientific and medical institutions of Ukraine and abroad has been analyzed.

**Evaluation of specific antiherpetic activity of Proteflazid<sup>®</sup> on preclinical studies.** Results of the antiviral activity in different dosage forms and pharmaceutical compositions based on the active substance preparation Proteflazid<sup>®</sup> are described in several papers [7, 8, 9]. Since Proteflazid<sup>®</sup> is a multicomponent mixture of natural compounds, in order to determine the specific activity of the individual compounds, the biologically active substance (BAS) of Proteflazid<sup>®</sup> preparation has been isolated. BAS is represented as a stable molecular complex compound of flavonoid aglycones: tricine, apigenin, luteolin, quercetin and ramnozine of O- and C-glycosides (which are located in a matrix of auxiliary natural substances).

S.L. Rybalko et al. (2010) studied the antiviral activity of BAS *in vitro* on a continuous culture of BHK cells. The authors noted that BAS inhibited herpes virus replication in dilutions ranging from 1:40 to 1:1280 (concentration from 12 mcg/ml to 0.37 mcg/ml). It showed the inhibition of the herpes virus infectious titer of more than 4.5 lg ID<sub>50</sub>. The values of the maximum tolerated concentration of BAS for BHK cells equal to 825 mcg/ml and the minimum active concentration of BAS to HSV-2 equal to

0.37 mcg/ml allowed them to set SI, equal to 2230, that indicated a highly selective BAS action on HSV-2 [10].

The study of BAS antiherpetic activity *in vivo* experiments were performed on a model of genital herpes virus infection in guinea pigs. The test preparations (BAS and acyclovir in ointment form) were applied to the scarified infected skin of guinea pigs 1 time a day for 5 days. The results showed that BAS had an antiviral activity with a more pronounced therapeutic effect (index of therapeutic action was 93.5%) than acyclovir ointment (index of therapeutic action was 56.0%) [10].

The mechanism of Proteflazid<sup>®</sup> antiviral action on DNA-containing viruses (which also include herpes viruses) is induced by inhibition of the virus enzymes synthesis such as thymidine kinase and DNA polymerase in infected cells, that blocks viral replication, in particular, even in case of acyclic nucleosides resistance [10, 11].

Besides the direct influence on viruses, Proteflazid<sup>®</sup> has a number of other properties. First, it induces the synthesis of endogenous  $\alpha$ - and  $\gamma$ -interferons and thus increases the nonspecific resistance to viral and bacterial infections, normalizes the immune status. It is important that during a prolonged daily use the preparation does not cause refractivity (hyporeactivity) of the immune system.

The preparation also prevents accumulation of lipid peroxidation products (inhibits free radical processes) and is a modulator of apoptosis, causing the death of infected cells. In the conditions of pre-clinical studies the teratogenic, mutagenic, embryotoxic, foetotoxic and carcinogenic effects of the preparation has not been reveal [10-13].

***Therapeutic efficacy and safety of the Proteflazid<sup>®</sup> (drops) against urogenital herpes virus infection.*** Confirmation of the wide poly-pharmacological effects of preparation in clinical practice had a great practical importance and was accompanied by a number of clinical studies to assess its efficacy and safety in the urogenital herpes pathology.

In 2000 B.M. Ventskovsky presented the results of a clinical study "Open Study on Tolerability and Preliminary Efficacy Evaluation of Proteflazid<sup>®</sup> (drop) in the Treatment of Primary and Recurrent Infections Caused by *Herpes Genitalis*". It was determined that Proteflazid<sup>®</sup> (drops) was highly effective in the treatment of primary and recurrent GH and did not cause serious side effects, compared to efficacy and tolerability of acyclovir [14].

I.B. Vovk et al. were among the first to publish data on the Proteflazid<sup>®</sup> (drop) effectiveness in gynecological practice (2002). Their study involved 68 women with chronic inflammatory genitals of chlamydial viral etiology (34 women with herpes infection (HSV-2) and 34 women with mix of herpes virus infections and genital chlamydial infection). There was a significant improvement in the clinical picture of the disease, normalization of the protective function in cervical mucus (slgA, lysozyme and complement component C3), reduction of genital tract contamination by pathogens: 1 month after treatment with Proteflazid<sup>®</sup>, the ELISA and PCR chlamydia in 88.2% women was undiagnosed using methods of microscopy; HSV-2 in 85.3% women was undiagnosed using PCR [15].

O.A. Andriets et al. (2004, 2005) studied the role of HSV-2 in the inflammatory processes of genital organs and therapeutic features of these disorders in prepubertal and pubertal girls. Proteflazid<sup>®</sup> (drops) was prescribed for the course up to 4 weeks only to the girls who had HSV-2 antigen (detected in smears). It was determined that after the 1st week of treatment the clinical manifestations and complaints were significantly decreased in 40% of patients, after 2 weeks of treatment rashes in the genital and subjective sensations completely disappeared in 85% of patients. During therapy the increase of the levels of IL-1 $\beta$ , IL-2, the PNP- $\alpha$  in peripheral blood and IL-1 $\beta$ , slgA in vaginal secret was observed. This effect persisted after the course of therapy that indicated the recovery and repair processes [16, 17].

In the same period S.V. Shvediuk (2003); I.T. Kishakevich (2005); O.V. Romashchenko et al. (2005) substantiated the expediency and confirmed the effectiveness of Proteflazid<sup>®</sup> (drop) in the treatment of inflammatory genitals diseases, including mixed infections. The similar positive data were obtained during researches. The appointment of the preparation was accompanied by positive changes in the local immunity, such as immunoglobulins and lysozyme in the cervical mucus level normalization, increase of slgA level and parallel decrease of IgM level, that indicated the activation of humoral immunity and reduction of the antigenic load, due to the reduction of genital infection. In the early days of the medication some patients had and exacerbation of the inflammatory process caused by the lysis of the microorganisms (that, in turn, had a positive effect on the effectiveness of antibiotic therapy), which then quickly stopped without any additional means. The positive dynamics was observed in more than 83.3% of the patients. The incidence of relapse was reduced to 5.0% [18, 19, 20].



In 2003-2005 T.M. Grinkevich conducted a series of studies on the effectiveness in different GH treatment regimen. It was confirmed that Proteflazid<sup>®</sup> (drops) eliminated the imbalance of cellular and humoral immunity, had a positive clinical effect, reduced the relapse rate by 19%, helped normalize vaginal microbiocenosis, accelerated re-epithelialization at herpetic endocervicitis [21, 22]. Similar data on the Proteflazid<sup>®</sup> (drops) for the treatment of herpes virus endocervicitis and cervical erosion were received by B.D. Lutsyk et al. (2003) [23].

Another author (O.M. Gopchuk, 2006) described the development of a comprehensive treatment method and preventive measures for the correction of neurohumoral menstrual disorders in patients with HVI based on Proteflazid<sup>®</sup> (drops). During the therapy, the researchers observed a normalization of the menstrual cycle, the lack of HSV-1 and HSV-2 detection within specific researches and restoration the vaginal microbiocenosis [24]. To continue the researches, in 2007 T.V. Gerasimova, O.M. Gopchuk presented the results of the Proteflazid<sup>®</sup> (drop) in the treatment of menstrual disorders caused by HVI and HPV infection. Proteflazid<sup>®</sup> was prescribed in combination with viferon. The duration of anti-relapsing treatment was 3-6 months. Clinical efficacy of the proposed treatment regimen was 82.8% and the recurrence rate of herpes infection fell by 2-3 times, HPV - 1.5-2 times [25].

In publications of 2006 and 2012 M.Ye. Zapolskiy presented data on clinical features and therapeutic efficacy of Proteflazid<sup>®</sup> (drops) in patients with GH complicated by erythema exudative multiforme (EEM). It was noted that in cases of uncomplicated GH, positive dynamics was observed as soon as on the 4-5 day of treatment and complete disappearance of symptoms - on 5-6 day. In the case of the EEM erosions and bullous elements epithelization in 96.9% of patients was stopped by the 9-10 day of treatment. Repeated EEM relapses within a year were noticed only in 12.5% of patients. The immunological parameters had a positive dynamics in the basic elements of cellular immunity and reduced the CIC [26, 27].

Similar studies were conducted by other authors. Thus, V.P. Fedotov et al. (2003), V.N. Lesovoy, Ye.V. Yakovleva (2006), I.G. Shimanskaya (2007, Belarus) evaluated the efficacy of the Proteflazid<sup>®</sup> (drop) in the treatment of patients with GH, including both symptomatic and asymptomatic forms. Positive clinical results in 95% of patients who received preparation were noted and 28.1% of patients observed a reduction of the duration and activity in clinical manifestations of relapses [28, 29, 30]. The preparation did not cause complications and was well tolerated.

According R.F. Ayzyatulov (2008), while taking Proteflazid<sup>®</sup> (drops) for the treatment of mixed urogenital infections in males, there was a positive clinical dynamics as soon as on the 3-5 day of therapy; on the 6-8 day discharge stopped and the majority of patients had elimination of the pathogen. Proteflazid<sup>®</sup> did not cause side effects and was well tolerated [31].

G.A. Flux (2008, Russia) confirmed the high efficacy Proteflazid<sup>®</sup> (drops) in patients with GVI. Positive clinical results were observed both during combined therapy in the GH treatment with using acyclovir and Proteflazid<sup>®</sup> monotherapy topically and systemically. There was noted a decrease in the frequency of exacerbations, normalization of laboratory parameters (it was shown the virus disappearance in the smears by PCR method and the reduction and/or disappearance of antibody titers by ELISA) during the acute manifestations of the GH and, most importantly, in remission. Side effects of the preparation were not identified during ongoing research [32]. The same research group (V.N. Serov et al., 2009) conducted an efficacy and tolerability studies of genital herpes infection with clinical signs and chronic relapsing course with associated mixed infection. It was shown that complex therapy with the Proteflazid<sup>®</sup> created conditions for the prevention and treatment of dysplastic processes of cervix, led to the normalization of humoral and cellular immunity, created favorable conditions for the treatment of associated urogenital diseases, which was much less sensitive to conventional antibiotic therapy. Improvement of psychosomatic indicators of patients, clinical picture of the disease, reduction of microflora contamination of the genital tract, normalization of the protective function in cervical canal had a positive effect on the local protection of urogenital system and the life quality of the woman and her family. Adverse reactions such as nausea, vomiting, intolerance phenomena during therapy were not observed [33].

In the meantime, A.V. Sundukov et al. (2008, Russia) conducted a clinical trial of the Proteflazid<sup>®</sup> (drops) in treatment of some HVI in adults. 22 patients with GH took Proteflazid<sup>®</sup> orally and topically as a lotion. During the GH therapy the preparation was highly effective and reduced the relapses in 8.2-8.4 times. Interrecurrent period was increased to  $144.5 \pm 14.8$  days in patients receiving Proteflazid<sup>®</sup> orally and topically, and to  $164 \pm 23,2$  days in the patients receiving Proteflazid<sup>®</sup> orally. It was proved that the preparation was well tolerated with minimal side effects [34].

V.A. Isakov, D.K. Ermolenko (2009, Russia) conducted an open, controlled clinical trial to determine the efficacy of Proteflazid<sup>®</sup> (drops) in the treatment of patients with recurrent GH. The high clinical efficacy of the preparation was proved: the relapse rate was reduced in 7.5 times, 32% of patients had no recurrence within a year. Averages of interrecurrent period increased in 2.8 times. Positive dynamics was observed in immunological parameters, too. After treatment using direct immunofluorescence method, herpes virus in 92% of patients was not detected during 6 months. The preparation was well tolerated, adverse reactions were not identified [35].

In 2011 M.G. Romanyuk et al. conducted an open, controlled, randomized study on the characteristics of treatment males with recurrent GH caused by HSV-2. During therapy with Proteflazid<sup>®</sup> (drops) positive clinical dynamics and epithelization were observed on the 6 day of therapy. The average number of relapses in patients was reduced from 6 times a year to 3 times a year. The authors compared the efficacy of the Proteflazid<sup>®</sup> with efficiency of famciclovir, but the frequency of adverse events in patients, who took Proteflazid<sup>®</sup>, was significantly lower [36].

In the same year, A.I. Baev et al. (2011) from Kazakhstan published a series of reports on the results of clinical studies. They investigated clinical and pathogenetic features, differential treatment therapy of mixed infections, which were transmitted sexually (STIs). According to the results of their observations, it was found that the use of the Proteflazid<sup>®</sup> (drops) in treatment of mixed STIs was an effective and safe method of treatment, which was confirmed by clinical improvement, normalization of immunological and biochemical parameters, lack of side effects and adverse reactions [37].

In further investigation P.P. Ryzhko, L.V. Roschenyuk (2012), P.M. Klimenko et al. (2012), L.M. Rak, O.M. Yuzko (2013) also noted the positive dynamics in the use of the Proteflazid<sup>®</sup> (drops). There was observed the regression of clinical manifestations, stable therapeutic response and reduction of the frequency of GH relapses in 1.5 times with reduction of their duration [38-40].

In 2015 A.G. Kornatskaya and V.A. Benyuk presented the results of two open, controlled, randomized, parallel clinical studies on comparative assessment of the efficacy and tolerability of Proteflazid<sup>®</sup> (suppositories), and Proteflazid<sup>®</sup> (drops in the form of vaginal tampon) in patients with herpes and urogenital viral and bacterial infection [41, 42].

A.G. Kornatskaya (2015) studied 70 women with verified diagnosis of genital herpes (HSV-1, HSV-2) in the acute stage. Based on the simple randomization the patients were separated into the main (n = 35) and control (n = 35) groups. Proteflazid<sup>®</sup> (suppositories) was assigned to patients of the main group, and Proteflazid<sup>®</sup> (drops) in the form of vaginal tampon with a solution of preparation was administered to patients of the control group. By the end of therapy and during the 8-week observation period a significant increase in the level of local immunity as compared with the initial (secretory IgA, lysozyme complement component C3) was observed. In particular, the level of the secretory IgA increased to the 10th day of treatment and remained definitely high over the 8-week observation period (from 990.45 to 1825.24 g/l); the level of lysozyme increased to the 10th day of treatment and remained definitely high over the 8-week period (from 28.39 to 41.31 g/L); the level of complement component C3 increased to the 10th day of treatment and returned to baseline by the end of the 8-week period (from 17.68 mcg/g of protein per screening to 81.17 mcg/g of protein on the 10th day and 20.37 mcg/g of protein on the 8-th week). After completion of the 10-day treatment and the 8-week observation period, there was a reduction in HSV viral load in DNA and a significant decrease in the level of markers HSV (IgG, IgM) compared to baseline [41].

Everyone involved in the study of woman reported the relief of the GH clinical manifestations. Efficacy of Proteflazid<sup>®</sup> (drops) treatment was 100% with no recurrence of herpes infection manifestations. During the research it was shown that the preparation Proteflazid<sup>®</sup> (drops) was highly effective and well tolerated. During the treatment no serious or unexpected adverse reactions were observed, laboratory parameters did not reveal any negative changes. The efficacy of Proteflazid<sup>®</sup> (suppositories) was equal to that of Proteflazid<sup>®</sup> (drops) in the form of vaginal tampon with a solution of the preparation which were used and stored very easily. It possessed an advanced level of compliance for the patients, was highly effective in case of a strict conformity to the rules of its application. Thus, the "suppositories" dosage form was more convenient for patients and did not cause adverse reactions locally [41].

Similar results were shown by V.A. Benyuk (2015) in a comparative clinical study of women with urogenital viral and bacterial infection. There were no cases of adverse changes in the objective data and laboratory examination, as well as

adverse reactions or side effects. Tolerability of treatment in all cases was interpreted as good [42].

Currently, there is a tendency to increase herpes virus infection in pregnant women [43]. Despite some advances in pathogenesis and treatment of this infection, the issues of accurate diagnosis, obstetrical tactic, disease prevention and treatment of pregnant women with HVI are still a matter of dispute. Therefore, significant perinatal losses and material costs of treatment prompt a lot of researchers to search for effective and economically viable methods of treating a viral infection in pregnant women.

Yu.P. Vdovichenko et al. (2003) showed that the Proteflazid<sup>®</sup> (drops) reduced the incidence of threatened abortion compared to the comparison group (from 73.3 to 36.7 %), placental insufficiency (from 46.7 to 23.3%), preeclampsia varying degrees of severity (from 23.3 to 10.0%), preterm delivery (from 16.7 to 6.7%), premature rupture membranes (from 46.7 to 20.0%) and anomalies of labor activity (from 26.7 to 10.0%) (the preparation was taken with the prophylactic treatment of pregnant women with latent and recurrent herpes infection). Furthermore, the authors noted positive aspects of the preparation, such as reduction of the frequency of newborn asphyxia varying degrees of severity (from 43.3 to 23.3%), intra-amniotic infection symptoms (from 23.3 to 10.0%) and absence of cases of generalized infection in newborns. Clinical efficacy was fully confirmed by virological, microbiological and functional methods of investigation [44].

Under the supervision of V.V. Simrok, Ye.V. Gordienko (2003) there were 34 women with diagnosed HVI and perinatal losses in history. It was shown that the use of the Proteflazid<sup>®</sup> (drops) produced good clinical and immunological effects. The clinical manifestations of these diseases were not revealed throughout the treatment and subsequently during pregnancy. This was confirmed by the results of serology. At the same time the pregnancy course had much less complications, including the development of placental insufficiency, and usually ended with delivery at term of the newborn in a satisfactory condition [45].

N.F. Nagornaya, S.V. Nikolaeva (2006, 2007) conducted a series of studies on the prevention, treatment and immunomodulating efficacy of Proteflazid<sup>®</sup> (drops) in monotherapy and in combination with acyclovir in patients with HVI suffering miscarriage. It was found that conducting of a differentiated pregravid preparation and treatment during pregnancy with the inclusion of Proteflazid<sup>®</sup> helped reduce

herpes infection recurrence and the risk of perinatal losses by 35%. The duration of relapse was reduced in 1.6-2 times, the recurrence rate decreased to 1-2 cases during 8 months. In the immunological parameters increase in the total number of T- and B-lymphocytes, normalization of T-cells population, decrease in the concentration of the CIC was observed [46-48].

G.V. Dolgova, V.G. Abashina (2009, Russia) confirmed the feasibility and effectiveness of prescribing Proteflazid<sup>®</sup> (drops) to couples of reproductive age with a history of pregnancy loss. During taking Proteflazid<sup>®</sup> by patients (within 28 days) allergic reactions to the drug were not reported [49].

V.A. Benyuk et al. (2012) analyzed the prevention and HVI treatment in pregnant women with metabolic syndrome. 30 patients received Proteflazid<sup>®</sup> (drop) to the standard regimen in pregravid period (during 3-6 months) and during pregnancy. During taking the preparation showed a significant decrease in clinical manifestations and shorter HVI recurrence (more than 1.4 times). Positive dynamics in the immunological parameters was determined, lower frequently (50% less) of obstetric and perinatal pathology was recorded. The frequency of abortion in the early stages fell from 73.3% to 36.7%, fetoplacental insufficiency from 46.7 to 23.3%. The usage of the preparation gave 2 times reduction of the incidence of disease in newborns [43].

E.I. Azimova et al (2011, Uzbekistan) obtained similar positive clinical and immunological results of the Proteflazid<sup>®</sup> (drop) in pregnant women. Proteflazid<sup>®</sup> was active against mixed viral-bacterial infections and reduced perinatal pathology [50].

As can be seen from the observations results presented above, currently Proteflazid<sup>®</sup> (drops) is widely used by practitioners in Ukraine as well as in Belarus, Russia, Kazakhstan, Uzbekistan. The preparation is a part of different treatment regimens for prevention of herpes viral and bacterial infections. Since receiving permission to use the Proteflazid<sup>®</sup> (drop) in clinical practice, over the past 15 years more than 37 clinical studies and observations were conducted on the study of the preparation efficacy and safety against herpes viral and bacterial urogenital infections (more than 1,900 patients who took the Proteflazid<sup>®</sup> (drops) were involved). The results of these observations are presented in the table.

**Table. The main results of the clinical studies on the efficacy and safety of the Proteflazid<sup>®</sup> (drop) in the period from 2000 to 2015**

№	Authors, year, source	Total number of patients / taking the preparation	The main results of the Proteflazid <sup>®</sup> (drops) usage in clinical practice.
1	Ventskovsky, 2000, [14]	60 / 40	Proteflazid <sup>®</sup> , in the treatment of primary and recurrent infections caused by <i>Herpes genitalis</i> , is highly efficient with no serious side effects. The complete elimination of the clinical manifestations was observed in 60% of patients on the 5-7th day of treatment, recovery of all patients occurred up to 10 days of treatment.
2	Vovk et al, 2002, [15]	68 / 50	Under the influence of the Proteflazid <sup>®</sup> the normalization in protective function of the cervical mucus (sIgA, immunoglobulins, lysozyme and complement component C3) was noted, the decrease in contamination of the genital tract by microflora, which favorably affects the state of local immunity in the female genital tract on the whole. According to the PCR data, the virus was not detected in 85.3% of women and IgM was absent in 91.2%.
3	Vdovichenko et al., 2003 [44]	120 / 30	Proteflazid <sup>®</sup> reduces the incidence of threatened abortion (from 73.3 to 36.7%), placental insufficiency (from 46.7 to 23.3%), preeclampsia of varying severity (from 23.3 to 10.0%), premature delivery (from 16.7 to 6.7%), premature rupture of membranes (from 46.7 to 20.0%) and anomalies of labor activity (from 26.7 to 10.0%).
4	Grinkevich, 2003 [21]	20 / 20	The Proteflazid <sup>®</sup> alleviates the disease, reduces the frequency of relapses, extends interrecurrent period. Increases the phagocytic activity of neutrophils, stabilizes cellular immunity.
5	Lutsyk et al., 2003 [23]	35 / 35	After treatment with the Proteflazid <sup>®</sup> clinical healing of cervical erosion in 15 patients out of 35 was noted. After treatment in 35 patients only individual cells infected with viruses were found. In 7 patients the disappearance of the symptoms of chronic fatigue, discomfort in the abdomen, often occurring before menstruation, was noted.
6	Simrok, Gordienko, 2003 [45]	34 / 19	For women, during complex HI and CMVI treatment on the eve of pregnancy, Proteflazid <sup>®</sup> contributed to the stabilization antibody levels to specific IgG level standards at the majority of the surveyed (for 8 of 11 pregnant patients) to the specific rules on the level at the priority of patients (for 8 pregnant out of 11 patients) due to the lack of Ig M in all 11 pregnant women. All pregnant patients of the main group had delivery on time with the 3340±55 g average weight of newborn in contrast to comparison group, which had average weight 2096±30 g.

7	Fedotov et al., 2003 [28]	34 / 34	Even a 2-3-days' treatment with Proteflazid <sup>®</sup> showed the stop in the appearance of new lesions, there was a tendency to epithelialization of erosions and a decrease in the severity of subjective sensations. Complete resolution of clinical manifestations was noted on 5-7th day of the administration of the preparation in 23 (69.1%) patients, on 8-9th day - in 11 (30.9%) patients. Clinical recovery was observed in 25 patients (70.9%) during Proteflazid <sup>®</sup> treatment and a significant improvement - in 9 patients (29.1%). Lack of effect or disease worsening during Proteflazid <sup>®</sup> usage was not marked.
8	Shvediuk, 2003 [18]	22 / 11	In the group of patients who was treated with Proteflazid <sup>®</sup> therapy alongside with accepted therapy, positive clinical picture was observed in 81.8% (in the control group - 72.7%), stable microbiological effects with chlamydia was marked in 90.9% (against 63.6% in the control), the frequency of recurrences of herpes lesions was observed in 18.2% patients. The side effects of the preparation both topically and orally were not found.
9	Andriets et al, 2004 [16]	20 / 10	Clinical symptoms and complaints were significantly reduced in 40% of female patients after the 1st week of dosing Proteflazid <sup>®</sup> , and rashes in the genitals and subjective sensations completely disappeared in 85% of female patients after a 2 weeks' treatment.
10	Kishakevich, 2004 [19]	170 / 31	After treatment with Proteflazid <sup>®</sup> the level of immunoglobulins and lysozyme in the cervical mucus was normalized, the level of sIgA significantly increased with parallel reducing the IgM level, which indicates the activation of humoral immunity and the reduction of the antigenic load due to the reduction of genital infection.
11	Andriets, 2005 [17]	116 / 42	Treatment with Proteflazid <sup>®</sup> led to the increase of IL-1 $\beta$ , IL-2, the PNP- $\alpha$ level in peripheral blood and IL-1 $\beta$ , sIgA in vaginal secretion during and after the course of treatment, which indicates the process of recovery and repair.
12	Romashchenko, Rudenko, 2005 [20]	60 / 30	Proteflazid <sup>®</sup> , in the treatment of genital inflammatory diseases caused by mixed infection, has more clinical, microbiological, immunological efficacy compared to traditional methods of treatment of such pathology. The incidence of disease recurrence during the basic therapy was 16.6%, but during Proteflazid <sup>®</sup> usage it was 5.0% ( $p < 0.05$ ).
13	Grinkevich, 2005 [22]	100 / 49	Under the treatment with the Proteflazid <sup>®</sup> the disbalance between cellular and humoral immunity was eliminated, clinical benefit was marked in 82.7% of cases, the reduction in the frequency of relapses by 19%; normalization of vaginal



			microbiocenosis in 83.6% of women, accelerating re-epithelialization at herpetic endocervicitis, decreasing psycho-emotional stress, lack of side effects.
14	Lesovoy, Yakovleva, 2006 [29]	54 / 30	The appointment of the Proteflazid <sup>®</sup> to men with genital herpes can significantly increase the effectiveness of the treatment by 15-20%. Furthermore, the positive effect is more sustained. The overall health of the patients is significantly improved, immunological indicators get normalized, the compensated clinical manifestations of herpetic prostatitis are observed.
15	Gopchuk, 2006 [24]	70 / 35	For women who had Proteflazid <sup>®</sup> therapy a significant increase in CD4+ lymphocytes and NK-cells to normal values was observed, the increase in the number of IFN- $\gamma$ and IFN- $\alpha$ , the indicators in the women immunogram were more positive, the normalization of the menstrual cycle, the absence of GH recurrence and normalization of vaginal microbiocenosis were noted.
16	Zapolskiy, 2006 [26]	30 / 30	Positive response was observed in all patients who took the Proteflazid <sup>®</sup> on 4-5th day of treatment, complete recovery - on 5-6th day for 70% of patients. It confirms the high efficacy in the treatment of genital herpes.
17	Nagornaya, Nikolaev, 2006, [46]	60 / 30	For patients who had habitual miscarriage with GH, Proteflazid <sup>®</sup> helps reduce the risk of recurrence and perinatal losses. The duration of relapse was reduced for the majority of patients in 1.6-2 times, the relapse rate - up to 1-2 cases within 8 months.
18	Ayzyatulov, 2006 [31]	30 / 30	Combined therapy with Proteflazid <sup>®</sup> against mixed urogenital infections for male patients is efficient, does not cause side effects, is well tolerated by the patients. Positive clinical dynamics was observed on 3-5th day of treatment; on 6-8th day discharge stopped, for the majority of patients the elimination of the pathogen was observed.
19	Nagornaya, Nikolaeva, 2007 [47]	80 / 40	For pregravid preparation and correction during pregnancy, for patients with chronic HVI and miscarriage, Proteflazid <sup>®</sup> helps correct the function of the immune system and reduce the antigenic load.
20	Nikolaeva, 2007 [48]	140 / 100	Women taking the Proteflazid <sup>®</sup> , demonstrated the correction of immunological disorders, improvement of the function of the fetoplacental complex. The reduction in the recurrence of herpes infection by 70%, in the frequency of threatened abortion by 55%, in placental dysfunction by 35%, in premature births by 29.5% and in total perinatal losses by 35% were noted.
21	Shimanskaya, 2007 [30]	32 / 32	As a result of treatment with Proteflazid <sup>®</sup> , 15 patients (46.9%) during therapy had no episodes of herpes recurrence, 9 (28.1%) had reduction in

			the duration of the activity and clinical manifestations, for 28 patients (87.5%) after the treatment of genital herpes, the virus was not detected by PCR, and also the virus was not identified for 7 patients with asymptomatic course of genital herpes.
22	Gerasimova, Gopchuk, 2007 [25]	150 / 150	Clinical efficacy of the proposed treatment regimen with Proteflazid <sup>®</sup> was 82.8%. During the treatment the acute inflammation was not observed, the biocenosis normalized. For 64% of women HSV was not found by PCR; recurrence of herpes infection decreased 2-3 times.
23	Sundukov, 2008 [34]	82 / 22	In the treatment of genital herpes Proteflazid <sup>®</sup> reduces the number of relapses 8.2-8.4 times, the interrecurrent period is increased more than 2.5 times.
24	Flaks, 2008 [32]	55 / 35	Under the influence of Proteflazid <sup>®</sup> therapy the reduction in the frequency of exacerbations was achieved, and also the normalization of laboratory values (the virus was not detected in the samples by PCR, the reduction and/or disappearance of the antibody titer by ELISA during the acute GH manifestations and period of remission (which is especially important) were noted.
25	Serov, 2009 [33]	102 / 72	After a course of combined therapy with Proteflazid <sup>®</sup> in patients fluctuations in local immunity did not extend beyond the physiological norm ( $p > 0,05$ ): catalase number reached $6,21 \pm 0,32$ units, SOD - $411 \pm 24,20$ , concentration immunoglobulins sIgA in the cervical mucus - $0,69 \pm 0,14$ g/l, IgG - $0,14 \pm 0,01$ , IgA - $0,11 \pm 0,01$ g/l, lysozyme - $0,15 \pm 0,21$ , complement component C3 - $0,071 \pm 0,01$ g/l which indicates a high efficacy of the treatment. For 98.61% of female patients the sensation of pain, itching disappeared, as well as the burning sensation in the site of the lesion, genital discharge was physiological in nature, fever or violation of general condition were not reported. After 14 days from the beginning of the complex therapy, 90.28% of the patients did not indicate the presence of headaches and muscle pain, tenderness, the inguinal and femoral lymph were not increased, there was no rash in the form of bubbles on the large and small labia, vaginal mucosa and cervix.
26	Dolgov, Abashin, 2009 [49]	68 / 68	After treatment, in the main group who took Proteflazid <sup>®</sup> the most favorable adaptive response (compared to baseline) was significantly increased by 60%. The changes in indicators of neutrophilic granulocytes after combined treatment with Proteflazid <sup>®</sup> testified to the growth of natural resistance in the main group of patients. It was shown that the introduction of the preparation significantly increased serum bactericidal and

			phagocytosis.
27	Isakov, Ermolenko, 2009 [35]	25 / 25	Patients who received therapy with the Proteflazid <sup>®</sup> demonstrated the relapse rate reduction by 7.5 times, had milder clinical relapses and 32% of patients had no recurrence during a year. The average interrecurrent period increased by 2.8 times. Positive dynamics was observed in immunological parameters. After a course of treatment for 23 patients (92%) by the DIF, herpes viruses were not identified during 6 months.
28	Asimov et al, 2011 [50]	60 / 30	Complex therapy with the Proteflazid <sup>®</sup> prevents the development of immunodeficiency, improves the function of the placenta, reducing obstetric and perinatal complications for women with recurrent herpes infection.
29	Romaniuk et al, 2011 [36]	580 / 312	During the therapy with Proteflazid <sup>®</sup> positive clinical dynamics was noted, epithelialization was observed on the average on 6th day of therapy (in the comparison group – on 8th day). The average number of relapses in patients was reduced from 6 to 3 times a year. The growth in the healing of herpetic lesions occurred in 26.1% of the cases, the disappearance of all GH symptoms was marked in 28% of the cases.
30	Baev et al, 2011 [37]	140 / 80	It was established that in treatment of mixed-STI Proteflazid <sup>®</sup> is an effective and safe preparation, which was confirmed by clinical improvement, normalization of immunological and biochemical parameters, lack of side effects and adverse reactions.
31	Zapolskiy, 2012 [27]	88 / 32	During EME therapy with the Proteflazid <sup>®</sup> the epithelialization of erosions and bullous elements was completed on 9-10 th day of treatment for 96.9% of patients of the main group. Repeated EME relapse within a year was observed for 12.5% of patients. In the HEME treatment Proteflazid <sup>®</sup> has immunocorrecting, antioxidant, detoxification effects, which is important in herpes-induced autoimmune processes.
32	Benyuk et al., 2012 [43]	90 / 30	In patients taking Proteflazid <sup>®</sup> the positive dynamics in the immunological parameters was noted, obstetric and perinatal pathology was recorded in less than 50% of cases. The frequency of abortion in the early stages fell from 73.3% to 36.7%, placental insufficiency fell from 46.7 to 23.3%; premature births - from 16.7% to 12.0%; premature rupture of the membranes - from 46.7 to 20%; anomalies in development of birth activity fell from 26.7 to 10%. The use of the preparation allowed to reduce the pathology in newborn 2 times: asphyxiation - from 43.3% to 23.3%; manifestations of intra-amniotic infection - from 23.3% to 10%; generalized infection - from 11.3% to 0%.
33	Ryzhko,	110 / 110	The monotherapy with Proteflazid <sup>®</sup> reduced the

	Roschenyuk, 2012 [38]		duration of the current recurrence an average from $7,7 \pm 0,1$ to $4,8 \pm 0,08$ days, in 85 (77.3%) patients was a decrease in the severity of the disease, as well as frequency relapse more than 2 times.
34	Klimenkoetal, 2012 [39]	40 / 30	During therapy with the Proteflazid <sup>®</sup> positive clinical dynamics (regression of lesions, reducing itching, burning) was observed on the average on 4th day, the reduction of relapse grew 1.5 times and the reduction in the frequency of relapses was noted.
35	Rak, Yuzko, 2013 [40]	64 / 32	During complex therapy with Proteflazid <sup>®</sup> positive dynamics in the regression of clinical manifestations was observed, as well as stable therapeutic response (through a month of observations) and the reduction in the frequency of relapses.
36	Kornatskaya, 2015 [41]	70 / 70	For women taking Proteflazid <sup>®</sup> , the increase in the secretory IgA level was observed by the 10th day of treatment, while IgA level remained significantly high during the 8-week period (from 990.45 to 1825.24 mcg/l); increased levels of lysozyme remained up to the 10th day of treatment, remaining significantly high during the 8-week period (from 28.39 to 41.31 mcg/l); the level of complement component C3 increased by the 10th day of treatment and returned to baseline by the end of the 8-week period (from 17.68 mcg/g of protein per screening to 81.17 mcg/g of protein on the 10th day and 20.37 mcg/g of protein on the 8th week). After the completion of a 10-days' treatment course, and after 2- and 8-weeks' observation periods, DNA HSV was not indicated in vaginal epithelium / cervix epithelium. All patients had significant (compared to baseline) reduction of the level of HSV marker (IgG, IgM) after 10 days of treatment and 2-and 8-weeks' observation periods.
37	Benyuk, 2015 [42]	70 / 70	A significant increase in local immunity was an important evidence of the therapy efficacy with Proteflazid <sup>®</sup> . In particular, the secretory IgA level and lysozyme level were increased by the 14th day of treatment, remaining significantly high throughout the observation period; the complement component C3 level increased on 14th day of the treatment and returned to baseline by the end of the 4-weeks' follow-up period (23.5 mcg/g of protein - on screening; 27.8 mcg/g protein – on 14th day; 22.4 mcg/g of protein - by the end of the 4-weeks' follow-up). It noted a significant (compared with baseline) reduction in viral load of DNA HSV. After completion of the 14-days' treatment and after completion of the 4-weeks' observation period, DNA HSV was no detected in smears from the vaginal epithelium/cervix epithelium. All patients had

			significant (compared with the outcome) reduction in the frequency of chlamydial DNA detection.
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### Conclusions

The results of pre-clinical study indicate the direct antiviral action of Proteflazid<sup>®</sup> (drops) against DNA viruses herpes. Proteflazid<sup>®</sup> has polypharmacological effect. It blocks the synthesis of virus enzyme DNA polymerase and thymidine kinase in herpes-infected cells, also induces the synthesis of endogenous  $\gamma$ - and  $\alpha$ -interferon, has antioxidant activity, has apoptosis-modulating effect, reinforcing the direct antiviral effect with a mediated antiviral activity.

A systematic review of research and literature, that concern the clinical use of the drug Proteflazid<sup>®</sup> (drops), confirmed its direct antiviral activity against herpes viruses, the validity of the pre-clinical results and proved the efficacy of the preparation in the genital herpes treatment, caused by viruses, in the clinical conditions.

A detailed analysis of the post-registration clinical results indicates a broad use of Proteflazid<sup>®</sup> (drops) in clinical practice of infectious diseases, gynecology, urology, and for the treatment of diseases caused by genital herpes.

Preclinical and clinical studies demonstrate that Proteflazid<sup>®</sup> (drops) contributes to the persistent therapeutic effect of herpes viruses eradication and reduce the incidence of recurrence, protect mucous membranes, normalizing local immunity (secretory immunoglobulin A, lysozyme and complement component C3).

On the basis of evidence-based material, it can be stated that Proteflazid<sup>®</sup> (drops) is the preparation that is ethiopathogenically justified in the treatment of urogenital infections caused by HSV with mixed infections (with oral and local application in the acute phase, during convalescence and persistence).

High clinical efficacy and safety are confirmed by the results the usage of Proteflazid<sup>®</sup> (drops) in the treatment of more than 1,900 patients (including pregnant women). 37 clinical trials with similar treatment direction were conducted. The preparation is well tolerated by the patients, has no serious side effects, and consequently does not require correction or cancellation of the treatment regimen.

Taking into account the high efficacy and safety of Proteflazid<sup>®</sup> (drops) in the genital herpes treatment, its usage is justified and introduced into guidelines and circulars in Ukraine and abroad [51-58].

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