

Ministry of health of the Republic of Belarus
Educational institution
«Gomel State Medical University»

Department of general and clinical pharmacology

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METHODOLOGICAL RECOMMENDATIONS

for a practical lesson on the discipline "Pharmacology"
for the third-year students of the Faculty of Foreign Students,
studying at the specialty 1-79 01 01 "General medicine"

**TOPIC 30: «ANTIMICOBACTERIAL, ANTISPIROCHETE,
ANTIVIRAL, ANTIFUNGAL DRUGS»**

Time: 3 hours

Approved at the meeting of the department of general and clinical pharmacology
the protocol № 18 of 30.06.2022

LEARNING AND EDUCATIONAL GOALS, OBJECTIVES, MOTIVATION FOR LEARNING THE TOPIC

This topic is the continuation of the section "Antimicrobial, antiparasitic and antiviral agents".

Tuberculosis, previously considered a disease of marginal people, nowadays isn't associated clearly with social status since it often develops due to backdrop of immunosuppressive therapy (for example, glucocorticoids in systemic connective tissue diseases). There is the similar situation with mycoses the systemic forms of which often accompany immunodeficiency states.

Viral diseases from respiratory infections to HIV are a frequent cause of hospitalization and taking of a sick leave that causes significant economic damage to the state. HIV is becoming more widespread, including our country. This disease is both of medical and social significance because a cautious attitude towards HIV-positive patients still remains in the society, including the doctors.

Syphilis is rare in the Republic of Belarus, however, individual cases are recorded annually. This disease requires long-term therapy considering the severity of its potential complications (for example, neurosyphilis).

All this necessitates knowledge of the pharmacotherapy of tuberculosis, superficial and deep mycoses, viral infections, including HIV, and syphilis.

Learning objective:

– systematize the knowledge of students on these topics. Be able to analyze the effects of medicines judging by their pharmacodynamic and pharmacokinetic properties, effectiveness and safety. Consider possible side effects of studied medicines, learn to justify the choice of anti-infectious agents. Prescribe studied drugs based on their pharmacodynamic and pharmacokinetic features taking into account the main pathology, concomitant diseases and the patient's age.

Educational purpose:

– to develop their value-personal, spiritual potential, to form the qualities of a patriot and citizen, ready for active participation in the economic, industrial, socio-cultural and public life of the country; to realize the social significance of their future professional activities, to learn to follow academic and work discipline, standards of medical ethics and deontology.

Tasks:

As a result of the study lesson, the student should

know:

- pathogenesis and clinic of tuberculosis, syphilis, HIV infection, the most common viral and fungal infections;
- pharmacological characteristics of antimicrobials, antiparasitic and antiviral agents;
- modern strategy of chemotherapy for tuberculosis, syphilis, mycoses and viral infections.

be able to:

- justify the choice of the drug taking into account the pharmacological characteristics of the drug and the individual characteristics of the patient;

- prescribe studied drugs.

possess:

- skills in choice of drugs on the topic of the lesson;
- the rules of prescribing the studied drugs in the treatment of various diseases and pathological conditions, taking into account the indications;
- skills of dosage regime correction in case of pathological changes in functions of organs or systems responsible for biotransformation and elimination of drugs or in case of joint use of different drugs;
- skills to search, analyze and summarize information about the use and effects of the studied drugs.

Motivation for learning the topic:

- the specifics of training doctors in this specialty determines the need for students to purposefully study the main pharmacological effects, providing therapeutic and preventive effects of drugs on the topic of the class, indications and contraindications for their use, the interaction of drugs, their combined use, which will successfully complete the specialized disciplines of the specialty.

MATERIAL EQUIPMENT

Reference and informational literature, charts, tables, presentations, drug collections.

CONTROL QUESTIONS FROM RELATED DISCIPLINES

1. Features of the structure and life activity of pale treponema. What are L-forms and when they are formed? Ways and mechanisms of infection with syphilis. Clinical picture of the periods of syphilis.
2. Types of mycobacteria. Prevention and early diagnosis of tuberculosis.
3. Features of vital activity of viruses. Stages of reproduction of viruses in the cell.
4. The problem of AIDS. Routes of transmission, periods of the disease, the problem of treatment. Prevention measures.
5. Features of the structure and reproduction of pathogenic and opportunistic fungi. Diseases caused by fungi.

CONTROL QUESTIONS ON THE TOPIC OF THE CLASS

1. Antituberculosis drugs: isoniazid, rifampicin, pyrazinamide, ethambutol, streptomycin, rifabutin, cycloserine, kanamycin. Basic and reserve funds for the treatment of tuberculosis. Principles of pharmacotherapy for tuberculosis, the concept of chemoprophylaxis.
2. Antileprosy agents (dapsone, clofazimine, rifampicin).
3. Antispirochete drugs.
4. Antiviral agents. Classification. Antiinfluenza drugs: rimantadine, oseltamivir. Antiherpetic drugs: acyclovir, idoxuridine, foscarnet. Drugs for the treatment of HIV infection: maraviroc, zidovudine, nevirapine, raltegravir, saquinavir, enfuvirtide. Anti-cytomegalovirus drugs (ganciclovir). Drugs for the treatment of respiratory syncytial infection: ribavirin, palivizumab. Interferons (interferon alpha, interferon alpha-2a, interferon alpha-2b, interferon beta, interferon gamma-1b) and interferonogens (tilorone,

arbidol). Mechanisms of action, principles of application, side and toxic effects of antiviral agents.

5. Antimycotic agents: amphotericin B, nystatin; griseofulvin, ketoconazole, clotrimazole, fluconazole, itraconazole. terbinafine. Classification, pharmacodynamics, spectrum of antifungal action, indications for use, side and toxic effects of antimycotics.

PROCESS OF THE STUDY

Theoretical part

Theoretical questions are described in the appendix to the methodological recommendations.

Practical part

1. Take notes on theoretical material demonstrated by the teacher.
2. Master the methods of solving the tasks and writing out prescriptions on the topic of the class.

Theme learning control

Conducted in the form of independent written work (solution of practical problems and prescriptions for individual task).

METHODOLOGICAL RECOMMENDATIONS FOR ORGANIZATION AND EXECUTION OF STUDENTS' INDEPENDENT WORK (SIW)

The time given for independent work can be used by students for:

- preparing for the practical classes;
- completing the tasks on the topic of the class in the workbook;
- preparing thematic reports, essays and presentations;
- taking notes from academic literature.

The main methods of organizing independent work:

- completing tests and practical tasks of the electronic educational-methodical complex (EEMC) for self-monitoring and self-assessment.

The list of tasks of the SIW:

- solving practical problems in the EEMC;
- completing the test tasks of the EEMC.

Control of the SIW is carried out in the form of:

- assessment of an oral answer to a question, report, report, or solution of a task in a practical class;
- individual conversation.

METHODOLOGICAL RECOMMENDATIONS FOR ORGANIZATION AND EXECUTION OF CONTROLLED INDEPENDENT WORK OF STUDENTS (CIWS)

Recommended forms of CIWS organization:

- doing exercises on the topic of the class in the workbook;
- writing an essay on a given topic;
- preparing a report and a multimedia presentation on a given topic.

The list of tasks of the CIWS:

Topics of essays / multimedia presentations:

1. The problem of resistance in the pharmacotherapy of tuberculosis (complete the teaching workbooks).
2. Provision of HIV-infected patients with antiretroviral medications: medical, social and economic aspects.

Forms of control of CIWS realization:

- checking and grading an essay on a given topic;
- checking and grading a multimedia presentation on a given topic.

LIST OF REFERENCES

1. Kharkevitch, D.A. Pharmacology: textbook for med. students: transl. of 12th ed. of Russ. textbook "Pharmacology" (2017) / D.A. Kharkevitch. - 2nd ed. - Москва: ГЭОТАР-Медиа, 2019. - 676 с.: ил., табл. - Рек. ФГАУ "ФИРО". – Режим доступа: <http://www.studmedlib.ru/book/ISBN5970402648.html> – Дата доступа: 23.05.2022.
2. Кратко о лекарственных средствах: учебно – методическое пособие для студентов 3 и 6 курсов факультета иностранных студентов, учреждений высшего мед. образования: в 2 ч.=Drugs in short: partical workbook for 3 and 6 year students Faculty for International Students of medical higher educational institutions: in 2 parts / Е.И. Михайлова [и др.]. – Ч. 1. – Гомель: ГомГМУ, 2020. – 56с. – Режим доступа: <http://elib.gsmu.by/xmlui/handle/GomSMU/7128> – Дата доступа: 23.05.2022.
3. Кратко о лекарственных средствах: учебно – методическое пособие для студентов 3 и 6 курсов факультета иностранных студентов, учреждений высшего мед. образования: в 2 ч.=Drugs in short: partical workbook for 3 and 6 year students Faculty for International Students of medical higher educational institutions: in 2 parts / Е.И. Михайлова [и др.]. – Ч. 2. – Гомель: ГомГМУ, 2020. – 76с. – Режим доступа: <http://elib.gsmu.by/xmlui/handle/GomSMU/7129> – Дата доступа: 23.05.2022.
4. Rang and Dale's Pharmacology / J.M. Ritter [et al.]. - 9th ed. - Edinburg [et al.]: Elsevier, 2020. - xvi, 789 p.: ill., tab. + Student consult online.

Antimycobacterial drugs are chemotherapeutic agents used to treat Mycobacteria infections (tuberculosis and leprosy) [1-15].

Classification	First-line drug				Second-line drugs	
Drugs	Derivatives of isonicotinic acid hydrazide	Derivatives of paraaminosalicylic acid	Antibiotics	Drugs of different chemical groups	Derivatives of isonicotinic acid thiamide	Antibiotics
	1. Isoniazid (H) 2. Phtivazide (Vanisid) 3. Fluenylidide	4. Sodium paraaminosalicylate (PAS) 5. Benzoyl-PAS-calcium (Bepask)	6. Sremptomycin sulfate (S) 7. Rifampicin (R)	8. Pyrazinamide (Z) 9. Ethambutol (E)	10. Ethionamide (Eto)	11. Cycloserine (Cs) 12. Ofloxacin (Ofx) 13. Levofloxacin (Lfx) 14. Amicacin (Am) 15. Kanamycin (Km) 16. Capreomycin (Cm)
Mechanism of action	1. Disturbance of mycobacterium cell membrane structure 2. Inhibits the synthesis of mycolic acid in the cell wall (1) 3. Inhibits metabolic and oxidative processes, the synthesis of nucleic acids (2) * <i>Bactericidal action</i> in reproduction (1) <i>Bacteriostatic action</i> (1-3)	1. Selectively compete with para-aminobenzoic acid (PABA) and inhibit the synthesis of folate in mycobacteria * <i>Bacteriostatic action</i>	1. 1. Supresses protein synthesis in the cell (6) * <i>Bacteriostatic action</i> 2. Inhibits DNA-dependent RNA-polymerase (7) * <i>Bactericidal action</i>	1. Inhibition of mycobacteriaL RNA synthesis * <i>Bacteriostatic action</i>	1. Blocks the synthesis of mycolic acid in mycobacteria * <i>Bacteriostatic action</i>	1. Disturbance of protein synthesis of the cell wall (11, 16) 2. See lesson № 29, "Antibiotics (end). Synthetic antimicrobial agents" (12-15)
Spectrum of activity	1. Mycobacterium tuberculosis 2. Chlamydia trachomatis (3)		See lesson № 29, "Antibiotics (end). Synthetic antimicrobial agents"	1. Mycobacterium tuberculosis 2. Mycobacterium leprae (10, 11) 3. E.coli, Proteus, cocci, causative agent of tularemia, etc. (11)		См. занятие № 29 (12-15)
Indications	1. Tuberculosis of various forms and localizations 2. Urogenital chlamydiosis (3) 3. Poor PASK tolerance (5)			1. Tuberculosis of various forms and localizations	1. Pulmonary tuberculosis resistant to the 1 st line drugs 2. Leprosy (10)	
Side effects	1. Dyspepsia (1,2) 2. Neurotoxicity (1,2) 3. Hepatotoxicity (1,2) 4. Hypovitaminosis B6 (1,2)	1. Dyspepsia 2. Hypothyroidism 3. Crystalluria, agranulocytosis (4) 4. Allergic reactions		1. Dyspepsia 2. Hyperuricemia (8) 3. Polyneuropathy (9) 4. ↓ vision, scotomas formation (9)	1. Dyspepsia 2. Headache, paresthesia 3. Allergic reactions	

Contraindications	1. Epilepsy and a tendency to seizures (1, 2) 2. Prior poliomyelitis (1, 2) 3. Violations of the functions of the liver and kidneys (1,2) 4. Hypersensitivity	1. Dysfunction of the liver and kidneys 2. Gastroduodenal ulcers 3. Myxedema 4. Cardiac insufficiency	See lesson № 29, "Antibiotics (end). Synthetic antimicrobial agents"	1. Dysfunction of the liver and kidneys 2. Epilepsy (8) 3. Gout (8) 4. Optic neuritis (9)	1. Dysfunction of the liver and kidneys 2. Gastroduodenal ulcers 3. Hypersensitivity	1. Psychoses, epilepsy (11) 2. Hypersensitivity 3. Impairment of kidney function	См. занятие № 29 (12-15)
NB!	<p>World Health Organization classification of drugs used to treat drug-susceptible and drug-resistant tuberculosis:</p> <p>First-line anti-TB drugs (Group 1) are currently recommended in a four-drug combination for the treatment of drug-susceptible TB. Second-line anti-TB drugs (Groups 2, 3 and 4) are reserved for drug-resistant TB. Third-line anti-TB drugs (Group 5) have unclear efficacy or undefined roles.</p> <p>First-line anti-TB drugs</p> <p>Group 1. Oral: isoniazid (H/Inh), rifampicin/rifampin (R/Rif), pyrazinamide (Z/Pza), ethambutol (E/Emb), rifapentine (P/Rpt) or rifabutin (Rfb).</p> <p>Second-line anti-TB drugs</p> <p>Group 2. Injectable aminoglycosides: streptomycin (S/Stm), kanamycin (Km), amikacin (Amk). Injectable polypeptides: capreomycin (Cm), viomycin (Vim).</p> <p>Group 3. Oral and injectable fluoroquinolones: ciprofloxacin (Cfx), levofloxacin (Lfx), moxifloxacin (Mfx), ofloxacin (Ofx), gatifloxacin (Gfx).</p> <p>Group 4. Oral: <i>para</i>-aminosalicylic acid (Pas), cycloserine (Dcs), terizidone (Trd), ethionamide (Eto), prothionamide (Pto), thioacetazone (Thz), linezolid (Lzd).</p> <p>Third-line anti-TB drugs</p> <p>Group 5. Clofazimine (Cfz), linezolid (Lzd), amoxicillin plus clavulanate (Amx/Clv), imipenem plus cilastatin (Ipm/Cln), clarithromycin (Clr).</p>						

Anti-spirochete agents – drugs for infectious diseases caused by spirochetes (syphilis, relapsing fever) and leptospira (leptospirosis) [1-15].

Antisymphilitic drugs

Classification	Antibiotics	Bismuth drugs
Drugs	<i>Basic:</i> 1. Benzathine benzylpenicillin (Extensillin, Bicillin-1); Bicillin-3, Bicillin-5 2. Benzylpenicillin sodium salt, novocaine salt <i>Alternative:</i> 3. Ceftriaxone 4. Doxycycline 5. Erythromycin	6. Biyohinol 7. Bismoverol
Mechanism of action	See lesson № 29, "Antibiotics (end). Synthetic antimicrobial agents"	Block SH-groups of enzymatic systems of spirochaetes
Pharmacological effects		1. Anti-spirochectis 2. Anti-inflammatory 3. Resolving effect
Indications		1. Different forms of syphilis (in combination with antibiotics) 2. Nonsyphilitic lesion of the central nervous system (arachnoencephalitis,
Side effects		1. Gingivitis, stomatitis, the appearance of a black line along the gums (bismuth line) 2. Hepato- and nephrotoxicity
Contraindications		1. Lesions of the oral mucosa 2. Kidney disease 3. Acute and chronic liver diseases with lesion of her parenchyma 4. Hemorrhagic diathesis
NB!	1) Primary syphilis of genital organs and other localizations therapy (outpatient care) <i>Basic method:</i> Benzathine benzylpenicillin – i/m, the 1 st injection – 4,8 mln IU i/m (2,4 mln IU for every glut), the 2 nd – 2,4 mln IU with 1 week interval. <i>Alternative methods:</i> Novocain salt of benzylpenicillin – i/m 600 thousand IU 2 paza/cyr (with 12 hours interval) - 14 days <i>or</i> Bicillin -3 – i/m 2,4 mln EД, <i>or</i> Bicillin-5 1,5 mln IU 3 times a week 6 injections, <i>or</i> Ceftriaxone - i/m 1,0 g once daily 14 days, <i>or</i> Doxycycline 0,1 g orally twice daily 20 days, <i>or</i> Erythromycin 0,5 g 4 times a day 20 days Children treatment is only inpatient. 2) Therapy of leptospirosis: Benzylpenicillin up to 18 000 000 IU daily 7 days <i>or</i> Ampicillin up to 6 g daily i/m or i/v 7 days, <i>or</i> Doxycycline 200 mg daily orally or i/v– 7 days, <i>or</i> Ceftriaxone 2 g daily 7 days.	

Antiviral drugs [1-15]

Antiviral drugs are medicines for the treatment and prevention of various viral diseases.

Classification	Anti-influenza agents	Antitherpetic, anticytomegalovirus agents	Antiretroviral agents	Agents for viral hepatitis
Drugs	1. Amantadine (Midantan) 2. Remantadine (Rimantadine) 3. Oseltamivir (Tamiflu) 4. Zanamivir (Relenza) 5. Arbidol	6. Acyclovir (Zovirax) 7. Valaciclovir (Valtrex) 8. Ganciclovir (Cymeven) 9. Idosukradin 10. Foscarnet	<i>NIRTs:</i> 11. Zidovudine (Retrovir) 12. Lamivudine (Zeffix) <i>NNIRTs</i> 13. Nevirapine (Viramune) <i>Protease inhibitors (PIs)</i> 14. Saquinavir (Invirase) 15. Indinavir (Crixivan)	16. Ribavirin <i>Interferons:</i> 17. Reaferon (Interferon- α2) 18. Intron-A (Interferon-α2b) <i>Interferon inducers:</i> 19. Cycloferon 20. Tylorone
Mechanism of action	1. Inhibit M2 proton channels of the influenza A virus (1, 2) and neuro-minidase of influenza A and B viruses → block viral replication (3, 4). 2. Prevents the fusion of viral lipid envelope with cell membranes, induces the synthesis of interferon (5).	1. Are phosphorylated in the infected cell with the formation of triphosphate derivatives → inhibit the synthesis of viral DNA-polymerase (6-8) 2. Violates the synthesis of nucleic acids (DNA), selectively depresses the replication of the herpes simplex virus (9) 3. Inhibits DNA polymerase and reverse transcriptase of HIV (10)	1. Inhibits the reverse transcriptase of viral DNA and selectively inhibits viral DNA replication (11,12) 2. Bind directly to reverse transcriptase of HIV → destruction of enzymatic catalytic center (13) 3. Inhibits proteases involved in the assembly of the viral virion at the exit from the affected cell (14, 15)	1. Inhibits synthesis of viral RNA and DNA (16) 2. Inhibit the synthesis of viral matrix RNA, suppress the synthesis of proteins of the viral envelope (17, 18) 3. Suppress the effect of tumor growth factors; destroy bacterial cells (17, 18) 4. Stimulate the synthesis of endogenous interferon in the body (19, 20)
Pharmacological effects	1. Antiviral , 2. Interferon-inducing (5,19,20), 3. Immunomodulating (5,17-20), 4. Antineoplastic (17,18), 5. Anti-inflammatory (19)			
Indications	1. Influenza A treatment (1-5,16) and prevention(5) 2. Influenza B treatment (3-5,16) 3. Herpes simplex virus type 1 and type 2 skin and mucosa infection (6-9), 4. Cytomegalovirus infection (6-8,10), shingles (6,7) 5. Acyclovir-resistant viral infections in AIDS patients (10)		1. Treatment of infection caused by HIV-1 and HIV-2 (11, 12, 14, 15); HIV-1 (13)	1. Хронический гепатит С (16-20) 2. Вирусные инфекции, вызванные RSV- вирусом (16) 3. Acute viral hepatitis B (16-20) 4. Kaposi's sarcoma (17,18)
Side effects	1. Nausea, vomiting (1-3) 2. Headache, dizziness (1-3) <i>Relenza (Zanamivir) – very rarely</i>	1. Nausea, vomiting (6-8,10) 2. Headache (6-8) 3. Anemia, granulocytopenia (8,10) 4. Inflammation or edema of the eyelids (9) 5. Nephro-, neurotoxicity (10)	1. Leukopenia, anemia (11, 12) granulocytopenia (11, 12, 13) 2. Dyspeptic phenomena (11-15), a taste perversion (15) 3. Peripheral neuropathies, myalgia (11-14)	1. ↓ blood pressure (16,18) 2. Thyroid dysfunction (16) 3. Leukemia and thrombocytopenia (16-18) 4. Flu-like condition 5. Allergic reactions
Contraindications	1. Diseases of the liver and kidneys (1-3) 2. Gastroduodenal ulcers (1) 3. Hypersensitivity to the drug	1. Hypersensitivity to the drug 2. Neutropenia, granulocytopenia, anemia (8)	1. Leukopenia, anemia (11, 12) 2. Chronic hepatitis and cirrhosis of liver, renal failure (11) 3. Hypersensitivity	1. Pronounced diseases of the liver and kidneys (16, 17) 2. Thyrotoxicosis (16) 3. Heart failure, decompensation (17,18)

NIRTs – nucleoside reverse transcriptase inhibitors, NNIRTs – Non-nucleoside reverse transcriptase inhibitors, HIV - human immunodeficiency virus, AIDS - acquired immunodeficiency syndrome, RSV - respiratory syncytial virus

Antifungal agents (antimycotics) [1-15]

Antifungal agents (antimycotics) — medicines that suppress the growth and reproduction of pathogenic fungi and are for the prevention and treatment of mycoses.

Classification	Polyene antibiotics and others *	Azoles	Allylamines	Derivatives of undecylenic acid
Drugs	1. Amphotericin B (Fungizone) 2. Nystatin 3. Levorin 4. Mycoheptin 5. Griseofulvin *	<i>Imidazole derivatives:</i> 6. Clotrimazole (Kanesten) 7. Ketoconazole (Nizoral) 8. Miconazole (Dactarine) <i>Triazole derivatives:</i> 9. Fluconazole (Diflucan) 10. Itraconazole (Orungal)	11. Terbinafine (Lamisil) 12. Naphthifin (Exoderyl)	13. Nitrofungin Neo 14. Undecine 15. MycoSeptin
Mechanism of action	1. Bind to ergosterol of the fungal membrane → ↑ its permeability → death of a fungal cell (1-4) 2. Inhibits the synthesis of nucleic acids → disrupts the reproduction of fungal cells (5)	Inhibition of the conversion of lanosterol to ergosterol (the main sterol of the cytoplasmic membrane of the fungal cells) → disruption of the formation of the fungal cell membrane	Inhibit the enzyme squalene epoxidase catalyzing (with the squalene cyclase) the conversion of squalene to lanosterol → ergosterol deficiency → squalene intracellular accumulation → death of the fungus	Bind to ergosterol fungal membrane → ↑ its permeability → death of a fungal cell
Pharmacological effects	1. Antimycotic effect: fungicidal action (1-4,6-12-15); fungistatic action (5-10,13-15), 3. antibacterial (3,6-10,12,13)			
Indications	1. Systemic mycoses: (blastomycosis, cryptococcosis, histoplasmosis, etc.) (1-4,7,9,10) 2. Candidomycosis (1-4,6,7,9,10) 3. Trichomoniasis (3,6) 4. Onychomycosis (5,7,10-12) 5. Dermatomycosis (trichophytosis, microsporia) (5-8,10-15) 6. Fungal eczema (13)			
Side effects	1. Nausea, vomiting 2. Dysfunction of the liver (1) 3. Impaired renal function (1,4) 4. Anemia, thrombocytopenia (1) 5. Candidiasis of the oral cavity (5)	1. Local reactions when applied to the skin (6,8) 2. Nausea, vomiting (7-10) 3. Arthralgia (7) 4. Dysfunction of the liver (7, 10) 5. Edema, dysmenorrhea (10)	1. Nausea, vomiting (11) 2. Neutropenia (11) 3. Local reactions when applied to the skin (12)	1. Topical reactions when applied to the skin (13, 14)
Contraindications	1. Diseases of the kidneys, liver (1,3-5) 2. Diseases of the hematopoietic system (1,5) 3. Diabetes mellitus (1,5)	1. Pregnancy, breast-feeding (6-9) 2. Dysfunction of the liver (7,8,10) 3. Herpetic fever (8) 4. Hypersensitivity to the drug	1. Severe renal and hepatic insufficiency (11) 2. Diseases of the blood (11) 3. Pregnancy, breast-feeding	1. Hypersensitivity to the drug 2. Acute inflammatory skin diseases (14,15)