Immunomax®

reinforces immunity
defends against infections
INSTRUCTION
on the Medical Use of Immunomax

Registration number: P No.001919/02-2002
Commercial name: Immunomax
Chemical name: acidic peptidoglycan having a molecular weight above 1000 kDa
Drug form: lyophilized powder, to be dissolved for intramuscular injections
Description: the drug is a white lyophilized powder
Composition: 100 or 200 U of Immunomax
Pharmacotherapeutic group: an immunomodulator
Pharmacological characteristics: Immunomax enhances the immunity to viral and bacterial infections. The immunopharmacological mechanisms underlying the effect of the drug are the activation of the following components of the immune system:

- NK cells, which intensively express CD69 activation molecules 2–3 h after Immunomax administration;
- circulating monocytes, which 2–4 h after the activation with Immunomax begin to secrete cytokines, including interleukin-8 and interleukin-1β, and tumour necrosis factor-α;
- neutrophilic granulocytes, the activation of which is mediated by monocytes; the drug has no direct effect on neutrophilic granulocytes. Interleukin-8 secreted by monocytes results in the activation of neutrophilic granulocytes, which becomes manifest 24 h after the Immunomax administration;
- tissue macrophages, in which morphology is altered, the production of bactericide substances is enhanced, and the 5′-nucleotidase activity is changed;
- a production of antibodies against soluble and corpuscular antigens.

Immunomax enhances protection against infections caused by viruses (human papillomavirus, herpes simplex virus, parvovirus, carnivore plague virus, etc.) or bacteria (colibacillus, salmonella, staphylococcus, chlamydia, mycoplasma, ureaplasma, etc.). This effect is expressed in adults and infants after the administration of the drug by various ways: intramuscularly, intravenously, intraperitoneally, or per os.

Pharmacokinetics of the drug has not been studied because of its peptidoglycan nature and very low effective doses.

Indications:
- for the correction of impaired immunity;
- for the treatment of pathological conditions (condylomas, warts, dysplasia, etc.) caused by human papillomavirus;
- for the treatment of infections caused by herpes simplex virus, chlamydia, mycoplasma, ureaplasma, and other bacteria and viruses.

Contraindications:
The drug should not be administered to persons with hypersensitivity to Immunomax.
Children under 12 years of age.

Pregnancy and lactation:
There are no data on the effect of Immunomax on pregnant women. Like other drugs, Immunomax should not be used during pregnancy unless the advantages for the patient overbalance the risk for the foetus.
Immunomax is not recommended to breastfeeding mothers.

Administration and doses:
The recommended dose for adults and children over 12 years of age is 100–200 U intramuscularly once a day. The contents of a vial (ampoule) is dissolved before use in 1 ml of water for injections and injected intramuscularly at a dose of 100–200 U, depending on the disease severity. The course of treatment consists of six injections on days 1, 2, 3, 8, 9, and 10 of treatment.

- For the treatment of recurrent anogenital warts, a course of six injections of 200 U Immunomax each is combined with the destruction of warts by one of standard methods: cryodestruction, electrocoagulation, laser destruction, or solcoderm.
- For the treatment of infections caused by bacteria or viruses, a course of six injections of 100-200 U Immunomax each is used.
- For the correction of a compromised immunity, a course of three to six injections of 100-200 U of Immunomax each is recommended.

Interaction with other drugs: Not described.

Side effects: Not found.

Form of manufacturing: The drug is manufactured in the form of white sterile lyophilized powder in vials or ampoules containing 100 or 200 U of Immunomax.

Shelf life: The shelf life is two years.

Storage conditions: The drug should be stored at a temperature from +4 to +8°C.

Retail conditions: Not to be sold without prescription.
**Natural killer cells activation**

**Immunomax is a powerful activator of NK cells.** In 2-3 hours of induction with Immunomax, NK cells massively express CD69, a cell activation marker. Cytolytic capacity of NK cells is increased 3-fold after activation with Immunomax.

**NK cells activation in vitro**

![Graph showing NK cells activation in vitro](image1.png)

**Lysis of myeloleukosis cells**

![Graph showing lysis of myeloleukosis cells](image2.png)

**Fig. 1.** NK cells activation in vitro. Donor peripheral blood was incubated in the presence of different concentrations of Immunomax.

**Fig. 2.** Influence of Immunomax on NK cell CD69-expression and cytolytic efficacy. Mononuclear fraction of human peripheral blood leukocytes was incubated for 3 hours in the presence of Immunomax (10 µg/ml) or recombinant human interleukin-2 (20 IU/ml).

**Fig. 3.** Multicolor flow cytometry detection of in vitro activated NK cells in the human blood.
Macrophages and monocytes

**Activation of tissue macrophages** is obvious by intensive generation of bactericide substances, cell morphology alterations and 5’-nucleotidase enzymatic activity suppression. **Monocyte activation and cytokine production.** In 2-4 hours after activation with Immunomax, monocytes start intensive secretion of interleukin-8, interleukin-1β, and tumor necrosis factor-α.

![Fig. 4. Enhancement of bactericidal efficacy of macrophages (peritoneal exudate cells chemoluminescence in response to zymozan) after preliminary incubation in presence of Immunomax.](image)

![Fig. 5. Enhancement of cytokines (TNF-α, IL-1β and IL-8) secretion by human monocytes incubated for 20 hours with Immunomax in vitro.](image)

![Fig. 6. Multicolor flow cytometry detection of intracellular interleukin-1β in human monocytes activated with Immunomax (in vitro).](image)
**Neutrophil granulocytes**

Neutrophil granulocytes are activated via monocytes since Immunomax has no direct activation effect on granulocytes. Interleukin-8 secreted by activated monocytes causes a postponed activation of granulocytes, which latter activation can be observed in 24 hours after induction with Immunomax.

Fig. 7. NK cells and granulocytes in vitro activation kinetics after incubation of the whole human peripheral blood in the presence of Immunomax (5 µg/ml).
Enhancement of antibody production against heterologous antigens

Immunomax significantly amplifies production of antibodies towards both corpuscular and soluble foreign antigens.

Fig. 8. The isotype of BSA-specific antibodies produced in mice after immunization with BSA plus Immunomax.

Fig. 9. An enhancement of BSA-specific antibody production in mice using Immunomax (1 µg/mouse).

Fig. 10. An enhancement of OVA-specific antibody production in mice using immunization with OVA plus Immunomax. A comparison with Complete Freund’s adjuvant (CFA) and synthetic lipopeptide.
Local purulent infection (abscess) in experimental animals

The experimental acute abscess was induced in guinea pigs by the subcutaneous inoculum of pathogenic bacteria, namely, 1.8 bln. *St. aureus* (strain 150) plus 1.8 bln. *E.coli* (strain 20). A conventional surgical procedure such as abscess dissection and sanitization (no antibiotics) when combined with Immunomax lead to a speedy clearance of the post-surgical purulent would and its accelerated healing.

The course of 3 consequent intramuscular injections of Immunomax was applied (40 U on every other day). Already in 2 days after the first injection of Immunomax, the load of *St. aureus* and *E.coli* within the purulent wound was 100-1000 times lower as compared to the one of the corresponding control without Immunomax.

**Cleaning *Staphylococcus aureus* from the abscess dissected and drained**

Fig. 11. The dynamics of *Staphylococcus aureus* load in the post-surgical purulent would during the treatment with Immunomax in comparison with the corresponding control treated without Immunomax.

**Cleaning *Escherichia coli* from the abscess dissected and drained**

Fig. 12. The dynamics of *Escherichia coli* load in the post-surgical purulent would during the treatment with Immunomax in comparison with the corresponding control treated without Immunomax.
Generalized lethal infections

Immunomax increases defense of experimental animals against acute infection diseases caused by viruses (human papillomavirus, herpes simplex virus, parvovirus, carnivore plague virus, etc.) or bacteria (colibacillus, salmonella, staphylococcus, chlamydia, mycoplasma, ureaplasma, etc.).

This effect is expressed in adult and infant animals after administration of the drug by various routes: intramuscularly, intravenously, intraperitoneally, or per os.

**Protection from Herpes simplex virus, type I**

![Graph showing survival of mice after challenge with 1000 LD₅₀ of Herpes simplex virus, type I after Immunomax administration.]

Fig. 13. A single injection of Immunomax protects up to 70% infected mice from their lethal challenge with 1000 LD₅₀ of Herpes simplex virus, type I.

Ordinate – Survival of mice after their challenge with 1000 LD₅₀ of Herpes simplex virus, type I;

Abscissa – dose of Immunomax (µg/mouse).

**Resistance against Salmonella thyphimurium**

![Graph showing ID₅₀ of Salmonella thyphimurium after Immunomax administration.]

Fig. 14. A single injection of Immunomax increases 5-7-fold the mouse resistance against a lethal challenge with Salmonella thyphimurium.

Ordinate – ID₅₀ of Salmonella thyphimurium;

Abscissa – dose of Immunomax (µg/mouse).
Human papillomavirus infection

In more than 90% patients, Immunomax prevents a recurrence of genital warts which are associated with Human papillomavirus infection and it leads to elimination of the virus in more than 50% patients. A course of 6 intramuscular injections in a dose of Immunomax 200 units each to be combined with a conventional destruction of genital warts.

Fig. 15. A disappearance of anogenital warts and prevention of the new warts recurrent growth after the treatment with injections of Immunomax – 200 U i/m every other day, 6 injections in total.

Fig. 16. Decrease of percent HPV-DNA positive patients according to PCR (Immunomax – 200 U i/m every other day, 6 injections in total).

Photo 1. Typical anogenital warts, associated with Human papillomavirus infection.
Herpes simplex virus infections

Treatment using Immunomax decreases frequency of outbreaks in recurrent genital herpes patients. A remission is prolonged 5-7-fold. Immunomax 200 units, intramuscularly, daily, N6. The second course - in 4 months.

Fig. 17. A decline in the frequency of genital herpes outbreaks after the treatment with Immunomax. Daily intramuscular injections of 200 U each, in total – 6 injections per a course of treatment. A repeated course (200 U i/m, N6) - in 4 months.

Photo 2. Typical herpes viral lesions of the skin.
**Urogenital chlamydia infection**

A use of Immunomax (200 U i/m, every other day, 3 injections in total) in a combination with the conventional protocol of treatment of the chronic Chlamydia urethritis, complicated with the prostatitis (doxicyclin, metronidazole, nistatinum, hyaluronidase, chemotripsin and prostate massage) lead to a clinical recovery of 90\% and etiological recovery of 96\% patients. The same treatment protocol without Immunomax lead to a clinical and etiological recovery only in 76\% and 88\%, respectively.

Fig. 18. A treatment efficacy of the chronic urogenital Chlamydia infection during its reactivation phase. Results of the complex treatment in a combination with Immunomax (red bars) or without it (blue bars) are represented. Clinical recovery means abrogation of the disease symptoms, and normalisation of urethral and prostatic secrete smears. Etiological recovery means elimination of Chlamydia from the urogenital tract according to the PCR test in 3 months after the treatment.
Chronic prostatitis

Immunomax significantly increases efficacy of antibacterial drugs in treatment of chronic urethrogenic prostatitis of different etiology (Chlamydia, Mycoplasma, Ureaplasma, Gram-negative bacteria, different coccal bacteria).

Intramuscular injections of 200U Immunomax on every other day (in total – 6 injections per a course) are recommended to be combined with the standard antibacterial treatment of prostatitis.

Fig. 19. Efficacy of treatment patients having chronic bacterial prostatitis with Immunomax (200 U, i/m, N6) in a combination with antibacterial drugs. Percent patients is shown who had clinical and etiological recovery after the treatment using antibacterial drugs with Immunomax (red bars) or without it (blue bars).
Immunomax in a combination with anti-protozoan drugs significantly increases efficacy of treatment of urogenital infection caused by Trichomonas vaginalis. 100% patients showed complete clearance from Trichomonas vaginalis after the treatment with Immunomax (200 U, i/m, daily, in total – 6 injections) in a combination with metronidazole. Along with that, the accompanying urogenital infections, in particular, Mycoplasma, Ureaplasma, Candida, Herpes simplex virus type 2 were also successfully eliminated from 70-86% patients.

**Clinical recovery**

![Clinical recovery graph](image)

**Etiological recovery**

(Percent of patients)

- **Trichomonas**: 100%
- **Mycoplasma**: 75%
- **Ureaplasma**: 70%
- **Candida**: 75%
- **Herpes**: 86%
- **Bacterial vaginitis**: 80%

Fig. 20. Immunomax (200 U i/m, daily, N6) increases efficacy of treatment of urogenital trichomoniasis with metronidazole. Ordinate – percent patients with clinical recovery.

Fig. 21. Clearance of accompanying infections after the treatment of trichomoniasis using Immunomax (200 U i/m, daily, N6) in a combination with metronidazole.
Purulent infections in patients (abscess, phlegmon, infected wound)

Immunomax (200 U, intramuscularly, N3) in combination with the standard surgical and antibacterial protocols significantly increases the efficacy of treatment:

- accelerates clearance of purulent wounds of infection agents
- accelerates formation of the granulation tissue and epithelisation of post-purulent wounds
- prevents formation of the rough deforming (cheloid) scar.

Fig. 22. Influence of Immunomax on the healing dynamics of the wound defect and on the quality of a newly forming scar. The dynamics of a leukocyte infiltration (histological attribute of the inflammation) and a refilling of the wound defect with the connective tissue: (a) in patients who have received only standard surgical and antibacterial treatment, an inflammation is continuously present within newly formed connective tissue; (b) in patients who have received 3 consequent injections of Immunomax (200 U intramuscularly, every other day) in a combination with the standard surgical and antibacterial treatment.

Photo 3. A histology of the purulent wound on day 9 of the standard surgical and antibacterial treatments without Immunomax (control group). A picture of the persistent inflammation within the newly forming connective tissue, the infiltration with polymorph leukocytes (H+E, x120).

Photo 4. A histology of the purulent wound on day 9 of treatment using Immunomax in a combination with the standard surgical and antibacterial treatments. A formation of a tender and well vascularised scar (H+E, x240).
Trophic ulcers

A use of Immunomax provides an effective treatment of trophic ulcers in patients with the chronic varicosity disease. The course of injections of Immunomax (200 U intramuscularly, every other day, in total – 3 injections) in a combination with standard methods of surgical and antibacterial treatment greatly promotes both ulcer’s clearance from the infection and accelerated healing.

![Graph showing ulcer size reduction with and without Immunomax treatment](image_url)

**Fig. 23.** An accelerated healing of the trophic ulcer under the treatment using Immunomax in a combination with standard surgical and antibacterial treatments. A dynamics of the ulcer size is shown during the treatment with or without Immunomax. Ordinate – the ulcerated surface relative size represented as the normalized value versus initial size of ulcer on day 0, at the start of treatment.

**Photo 5.** The trophic ulcer of the shin by a chronic varicosity disease.