

Link to the website of the medical registry:

(<http://reestrinform.ru/reestr-clinicheskikh-issledovaniy/id-5405.html>)

Name of medical device:

Hydrogel coating to suppress the development of bacterial biofilms

ENTOMIX® according to TU 21.20.23-006-72500079-2017

***Results from the clinical trial of ENTOMIX will be published in an official
Scientific Publication in an American Journal by May 2020***

Results of clinical trials of a hydrogel coating ENTOMIX

Bacterial skin lesions are a group of diseases most commonly encountered in dermatological practice. Pyoderma is one of the most common skin diseases; in some cases, they can lead to sepsis. Pyoderma treatment is carried out mainly with the help of topical agents, however, complications associated with the appearance of microorganisms resistant to antimicrobial drugs used in therapy are not uncommon.

Chronic skin diseases such as trophic ulcers are particularly important in dermatology. Unlike acute infectious processes, they require long-term therapy. Difficulties in treating such complications are associated with a wide range of pathogenic microorganisms, including those capable of forming a biofilm on the surface of the wound, which can seriously reduce the effectiveness of antibiotic therapy.

Burns are one of the most common traumatic injuries in the world. A feature of a burn wound is destruction of the structure of the skin, this mainly determines the severity of its course and the inevitability of its seeding by microorganisms. However, the active use of antibiotics in the treatment of infected burns contributes to the development of resistance of pathogenic microflora. A special role is played by biofilms. An active search is underway for agents that

prevent the transition of bacteria to this form of resistance and effectively eliminate already formed biofilms.

Currently, Entomix can effectively cope with all of the above infectious skin lesions. This is evidenced by the results of clinical trials and approbations.

ENTOMIX® is a hydrogel coating for the suppression of bacterial biofilms, designed to treat and prevent infectious skin diseases, as well as to accelerate the regeneration of damaged skin areas. The main active ingredient of Entomix is the FLIP7 complex, which contains cationic peptides of natural origin (defensins, cecropins, diptericins, proline-rich peptides). FLIP7 prevents the formation and effectively fights bacterial biofilms formed by *Staphylococcus aureus*, *Escherichia coli* and other pathogens that populate wounds and damaged areas of the skin and mucous membranes. In this case, FLIP7 acts on both sensitive and antibiotic-resistant bacteria, and does not cause resistance development. The gel-forming component of Entomix is a copolymer of acrylic acid carbopol, which is widely used in medical wound dressings. The interaction of FLIP7 peptides with Carbopol creates an integrated wound dressing that provides mechanical protection for the damaged surface, sterilizes the wound, and accelerates tissue regeneration.

Entomix gel treatment of **chronic recurrent pyoderma** allowed to improve the condition in all patients (15 people). In a clinical study, Entomix was applied to the affected area 1-2 times a day for 7 days. As a result, by the 7th day of observation, 11 out of 14 patients (78.0%) had no infiltration detected in the primary screening. In all 15 patients (100%) erythema, weeping, and swelling disappeared. Peeling was absent on the 7th day in 9 of 12 patients (75.0%). By the 7th day, a statistically significant decrease in the average area of pyoderma from 4.0 to 1.3 cm² was found, what is 67.5%. If before treatment the average number of microorganisms in the wound was 100 x 10³ CFU, after treatment there was a statistically significant decrease in the level of this indicator to 1 x 10³ CFU.

It is important to note that the reduction in microbial load was achieved without antibiotics. Parallel monitoring of the patient's condition, such as clinical blood test, body temperature and blood pressure, did not reveal any deviations from standard values. There were also no unpleasant subjective sensations after applying Entomix, such as burning and itching.

The effectiveness of Entomix was compared with the published results of clinical trials of drugs used to treat pyoderma. In total, 8 comparison groups with a total number of 1879 of people were available. Patients of all comparison groups received complex treatment: mechanical removing devitalized tissue from a wound bed (surgical debridement) + application of antimicrobial dressings, or oral administration of co-trimoxazole. A comparative analysis of the therapeutic efficacy of Entomix in patients with pyoderma has shown that its effectiveness generally exceeds the effectiveness of surgical debridement and other drugs (Table 1 in the Appendix). The maximum benefits are found by comparing Entomix with such well-known means as wound dressings with silver or iodine ions.

In a clinical study evaluating the effect of Entomix on the process of **ulcer regeneration in diabetes** in 10 patients, Entomix was applied to the affected area once a day under a bandage for 7 days. A decrease in the size of the ulcer by the 7th day from the start of treatment was observed in 6 of 10 patients. In the remaining 4 patients measurable changes in the ulcer area were not noted, however, 3 of them showed an objectively observed improvement (decrease in the sum of points characterizing the intensity of the wound process from 6-7 to 3-5 with a simultaneous increase in the number of points characterizing the degree of ulcer epithelization from 0 to 2 points). Another patient from this group showed a decrease in the sum of points characterizing the intensity of the wound process from 6 to 5 points and an improvement in the cytological picture of wound exudate (a decrease in leukocytosis from 4 to 2 points and an increase in the number of fibrocytes from 1 to 2 points). Thus, a 7-day course of Entomix treatment provided a therapeutic effect, estimated by the sum of indicators of the early stage of treatment, in 100% of patients.

At the same time, there was a tendency toward a decrease in the total concentration of pathogenic microorganisms in the exudate from an average of 6.0×10^6 to 0.6×10^6 CFU ($P < 0.05$). Monitoring of the patient's condition (clinical blood test, body temperature, blood pressure) did not reveal any deviations from the normative values.

The results obtained during the observation of 10 patients with diabetic ulcers were compared with literature data. Analysis method: comparing the rate of decrease in the area of the ulcer surface in the treatment of Entomix and known wound dressings. The results are presented in table 2 (in the Appendix). The use of Entomix accelerated the healing rate of a diabetic ulcer compared to known wound dressings and surgical debridement. Table 3 (in the Appendix) summarizes the results of 13 clinical trials considered in table 2. In total, 596 patients took part in these trials.

The average ulcer healing rate using known wound dressings and surgical debridement methods was 0.79% per day. The use of Entomix provided a statistically significant increase in the healing rate of ulcers. If extrapolate the available data, the average time to achieve complete ulcer epithelization can be reduced from more than 4 months using known medical devices and surgical debridement methods to less than 2 months when using Entomix. Unlike all known products, the Entomix hydrogel wound dressing most closely matches the principles of the TIME (tissue, infection/inflammation, moisture balance and edge of wound) concept, developed by an international team of experts for the treatment of open chronic wounds and ulcers healing by secondary tension. Entomix provides moisture balance restoring due to the hydrogel base and does not interfere with proper aeration, inhibiting the growth of pathogenic microflora. It is also important to note that Entomix, thanks to the antimicrobial complex FLIP7, is the only agent that contains a component with proven antibiofilm activity.

In 20 patients with **burns complicated by a bacterial infection** (skin, mucous membranes) high efficiency of Entomix was also shown. In a clinical study Entomix was applied to the affected area once a day under a bandage for 7 days. At the same time, basic therapy with 100 mg of doxycycline was used. Entomix treatment was started on 4-6 days after receiving a burn. Efficiency criteria were: the dynamics of the infectious process in patients with pathogens resistant and sensitive to doxycycline, the number of patients with complete re-epithelization on the 7th day of treatment and the timing of re-epithelization.

The results showed that treatment of the wound surface with Entomix plus oral doxycycline provided fast (within 3 days of treatment) and complete purification from pathogenic bacteria, including *Staphylococcus aureus*, coagulase-negative staphylococcus, *Enterococcus* spp, *Klebsiella pneumoniae*, *Corynebacterium* spp, *Streptococcus*. Treatment with Entomix and oral doxycycline was equally effective in patients infected with both sensitive and resistant to doxycycline forms of pathogens. In these two comparison groups, the same rates of elimination of pathogens and re-epithelization of the wound surface were observed. The doxycycline-resistant isolates found in the participants of the clinical trial were also resistant to other antibiotics (multidrug-resistant forms). This did not affect the effectiveness of Entomix treatment.

The used Entomix treatment regimen provided complete re-epithelization of the wound surface in 16 out of 20 patients. For comparison, the timing of re-epithelialization in the treatment of Entomix and the comparison drug, 1% silver sulfadiazine cream (SSD), was considered (table 4 in the Appendix). The average period of re-epithelialization in the treatment with a SSD was calculated based on the average values of this indicator in series of 17 independent clinical trials (1319 patients in total). Comparison showed that Entomix caused a significant and statistically highly reliable ($P < 0.001$) reduction in re-epithelialization time compared with an SSD. Entomix treatment provided complete re-epithelization of the wound surface in 16 out of 20 patients, 48% faster than the average re-epithelialization time in SSD

clinical trials ($P < 0.001$). Considering 4 patients with incomplete epithelization by the 7th day of treatment, the average duration of epithelization in the whole group of patients treated with Entomix decreased by 44% (by 5.6 days) compared with SSD treatment ($P < 0.001$).

The analysis of the mean time of epithelization and the number of patients with complete epithelization by the 7th day clearly shows the advantage of Entomix over standard wound dressings (table 5 in the Appendix). It should also be noted that higher efficacy rates of Entomix were obtained with treatment starting from 4-6 days after the burn, while SSD treatment began from 1-2 days after the burn. Also, the treatment time for Entomix was 7 days, and SSD treatment was at least 16-17 days.

CONCLUSIONS

1. Entomix hydrogel coating for the suppression of bacterial biofilm meets the highest standards of safety for dermatological products. Hitherto no side effects of Entomix have been described.
2. Entomix hydrogel coating is an effective and safe treatment for pyoderma. The effectiveness of Entomix generally exceeds the effectiveness of surgical debridement and other means. An important advantage of Entomix is the ability to treat pyoderma without antibiotics and surgical intervention.
3. Entomix hydrogel coating provides effective treatment of diabetic foot ulcers in accordance with the principles of the TIME. It provides moisture balance and reduction of microbial load in the wound, which, in accordance with the TIME concept, is an important condition for healing. Entomix provides a rapid reduction in ulcer surface area within 7 days from the start of treatment. In terms of the ulcer reduction rate, Entomix exceeds the indicators of known wound dressings and surgical debridement methods obtained in 13 clinical trials, the results of which are published and available for comparative analysis.

4. Entomix hydrogel coating is effective and safe for the treatment of burns infected by both resistant and antibiotic-sensitive bacterial pathogens. Entomix treatment provided complete re-epithelization of the wound surface by 48% faster than a standard wound coverage SSD. The mean time to complete epithelization and the number of patients with complete epithelization by the 7th day clinical trials showed the advantage of Entomix over standard wound dressings.

ATTACHMENTS

Table 1. Therapeutic efficacy of Entomix and comparison drugs in patients with pyoderma.

Treatment option	Criteria of effectiveness	Treatment Time (days)	N	Comparison drug	Entomix	P	Clinical trial number
Aquacel Ag (wound dressing) Iodoform wound dressing	Improvement of the condition (decrease in lesion surface area $\geq 30\%$)	14	49 43	19 (44,2%) 6 (14,0%)	14 (93,3%)	0,002 <0.001	NCT00829686
Providence (povidone iodine) + Surgical Debridement (SD) SD	Improvement of the condition (reduction of the area of damage, erythema, purulent discharge)	7	51 46	45 (88.2%) 42 (91.3%)	15 (100%)	0,367 0,540	NCT02600871
Bactrim (Trimethoprim - sulfamethoxazole) tablets + SD SD	Worsening of the condition (increased area and intensity of damage)	7	96 116	15 (15,6%) 27 (23,3%)	0	0,216 0,079	NCT00973765
Trimethoprim-sulfamethoxazole + SD SD	Improvement of the condition (reduction of erythema, edema, compaction)	14-21	630 617	507 (80,5%) 454 (73,6%)	15 (100%)	0,116 0,045	Gottlieb 2017, 19(4), 308-311
Trimethoprim-sulfamethoxazole (tablets) + SD SD	Clinical improvement	7	18 13	14 (77,8%) 10 (76,9%)	15 (100%)	0.156 0.212	NCT00829686

Table 2. The healing rate of diabetic foot ulcers when using Entomix and known wound dressings and coatings

Wound dressings and coatings	N	Ulcer size reduction, %/day	% to Entomix	P	Clinical trial number /Publication
Entomix	10	2,04±0,562	100		
Santyl ointment	28	0,73±0,114	36	0,001	NCT01408277
Santyl ointment	51	1,37± 0,177	67	0,158	NCT02581488
Santyl ointment	29	1,21±0,25	59	0,130	NCT01143714
Santyl ointment	24	1,60±0,607	78		NCT01056198
Silver ion wound dressing	51	0,98±0,194	48	0,039	NCT02581488
Aquacel Ag wound dressing	145	0.89 ± 0.938	44	0,749	Harding et al, 2012
Urgotul Silver Wound Cover	136	0,76 ± 1.071	37	0,747	
Urgotul Silver Wound Cover	102	0,85	42		Lazareth et al, 2008
Urgotul wound dressing		0.10	5		
Gauze Dressing with Vaseline	30	0,83 ± 0,704	41	0,247	Ahmed, Ahmed 2014
Gauze dressing + SD	27	0,55±0,218	27	0,005	NCT01408277
Gauze dressing + SD	28	0,39±0,085	18	0,000	NCT01143714
Gauze dressing + SD	24	0,03±2,043	1,5	0,535	NCT01056198

Table 3. Average values of the healing speed of a diabetic foot ulcer when using Entomix and known wound dressings and coatings (based on table 2).

Drug / method of treatment	Reducing the area of the ulcer,		P (ANOVA)	The predicted average period of complete ulcer epithelization, months
	%/day	%		
Entomix (n-10)	2,04 ± 0,562	100		1,6
Average for all comparison groups (n = 13)	0,79 ± 0,127	39	0,02	4,2

Table 4. Average re-epithelialization period from the getting a burn in the treatment of Entomix and SSD

Drug	Number of Patients (N)	Time to complete re-epithelialization (M ± m), day	Clinical trial number/ Publication	
Entomix (complete re-epithelialization)	16	12.31±0.218	Clinical trial reports	
Entomix (all patients)	20	12.68 ± 0.307		
SSD	82	18 ± 0,706	NCT01439074	
	52	17 ± 0.667	Wasiak et al., 2013	
	35	13.7± 0.727	-----'-----	
	17	30.9± 1.795	NCT01553708	
	34	12 ± 6	Muangman et al., 2009	
	328	18.3 ± 22.3	Cuttle et al., 2007	
	755		29.28	Maciel et al., 2019 (average values for 11 trials included in the meta-analysis).
			21.53	
			11.3	
			15.49	
			12.2	
			15.82	
			13.7	
		17.5		
	21.53			
	24.24			
	18.8			
Average for 17 SSD trials	1319	18.3±1.38	P _{Entomix-SSD} <0.001	

Table 5. The number of patients with complete re-epithelialization of the burn on the 7th day from the start of treatment

Drug	N	Number of patients with complete re-epithelialization, %	P (Z-test)	Source of information
Entomix	20	80		
SSD	82	27	<0.001	NCT01439074
SSD	52	11.5	<0.001	Wasiak et al, 2013

PHOTO GALLERY 1, Diabetic Foot Ulcers

Patient No: 001

Gender: Female, **Age** 48

Localization of a diabetic ulcer: left foot

DAY 1:



DAY 7:



Patient No: 002

Gender: Female, **Age** 57

Localization of a diabetic ulcer: right foot

DAY 1



DAY 7



Patient No: 003

Gender: Man, Age 80

Localization of a diabetic ulcer: right foot

DAY 1



DAY 7



Patient No: 004

Gender: Female, **Age** 36

Localization of a diabetic ulcer: right foot plantar surface

DAY 1



DAY 7



Patient No: 005

Gender: Female, **Age** 74

Localization of a diabetic ulcer: back surface of the left foot

DAY 1



DAY 7



Patient No: 006

Gender: Male, **Age** 88

Localization of a diabetic ulcer: lateral surface of the 4th finger of the left foot
DAY 1



DAY 7

Patient No: 007



Gender: Female, Age 55

Localization of a diabetic ulcer: cleft calcaneal region

DAY 1



DAY 7



Patient No: 008

Gender: Male, **Age** 82

Localization of a diabetic ulcer: plantar surface of the main phalanx of the 1st finger of the left foot

DAY 1



DAY 7



Patient No: 009

Gender: Female, **Age** 70

Localization of a diabetic ulcer: distal phalanx of the 1st finger of the left foot
DAY 1



DAY 7



Patient No: 010

Gender: Male, **Age** 66

Localization of a diabetic ulcer: on the dorsum of the right foot in the 5th metatarsophalangeal joint

DAY 1



DAY 7



PHOTO GALLERY 2, BURNS

Patient No: 001

Gender: Male, **Age** 19

Localization of a burn wound: Household front burn with the transition to the inner surface of the upper third of the thigh.

DAY 1



DAY 4



DAY 7



Patient No: 002

Gender: Male, **Age** 31

Localization of a burn wound: Industrial burn of the right foot, back surface.

DAY 1



DAY 4



DAY 7



Patient No: 003

Gender: Male, **Age** 31

Localization of a burn wound: Household burn of the foot.

DAY 1



DAY 4



DAY 7



Patient No: 004

Gender: Male, **Age** 31

Localization of a burn wound: Household burn of the right upper limb.

DAY 1



DAY 4



DAY 7



Patient No: 005

Gender: Male, **Age** 50

Localization of a burn wound: Household burn of the right upper limb (forearm).

DAY 1



DAY 4



DAY 7



Patient No: 006

Gender: Male, **Age** 60

Localization of a burn wound: Household burn of the inner surface of the left foot and ankle joint.

DAY 1



DAY 4



DAY 7



Patient No: 007

Gender: Male, **Age** 62

Localization of a burn wound: Household burn of hands

DAY 1



DAY 4



DAY 7



Patient No: 008

Gender: Male, **Age** 52

Localization of a burn wound: Household burn of the front surface of the body.

DAY 1



DAY 4



DAY 7



Patient No: 009

Gender: Male, **Age** 38

Localization of a burn wound: Household burn of the left thigh (upper third)

DAY 1



DAY 4



DAY 7

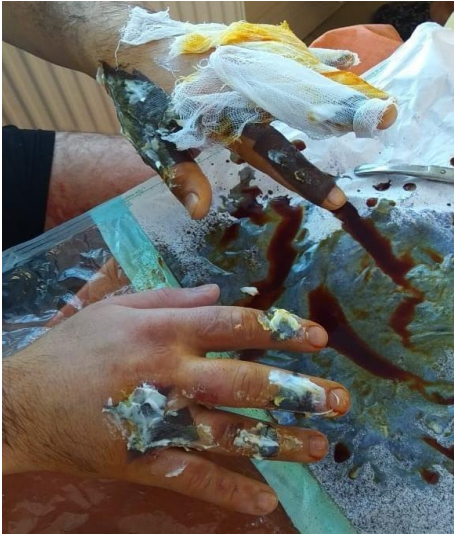


Patient No: 010

Gender: Male, Age 27

Localization of a burn wound: Household burn of hands

DAY 1



DAY 4



DAY 7



PHOTO GALLERY 3, PYODERMA

Patient No: 001

Gender: Female, **Age** 29

Pyoderma localization: back skin.

DAY 1



DAY 7



Patient No: 002

Gender: Male, Age 40

Pyoderma localization: scalp.

DAY 1



DAY 7



Patient No: 003

Gender: Male, Age 59

Pyoderma localization: sacrum.

DAY 1



DAY 7



Patient No: 004

Gender: Male, **Age** 25

Pyoderma localization: brush skin.

DAY 1



DAY 7



Patient No: 005
Gender: Female, **Age** 20
Pyoderma localization: face skin.

DAY 1



DAY 7



Patient No: 006

Gender: Male, **Age** 49

Pyoderma localization: lower limbs.

DAY 1



DAY 7



Patient No: 007

Gender: Female, **Age** 51

Pyoderma localization: upper limb skin.

DAY 1



DAY 7



Patient No: 008

Gender: Male, **Age** 30

Pyoderma localization: face skin.

DAY 1



DAY 7



Patient No: 009

Gender: Female, **Age** 46

Pyoderma localization: brush skin.

DAY 1



DAY 7



Patient No: 010

Gender: Male, **Age** 32

Pyoderma localization: face skin.

DAY 1



DAY 7



Patient No: 011

Gender: Male, **Age** 26

Pyoderma localization: skin of the face, neck, back.

DAY 1



DAY 7



Patient No: 012

Gender: Male, **Age** 23

Pyoderma localization: face skin.

DAY 1



DAY 7



Patient No: 013

Gender: Female, **Age** 49

Pyoderma localization: skin of the perioral region of the face.

DAY 1



DAY 7



Patient No: 014

Gender: Male, **Age** 18

Pyoderma localization: back skin.

DAY 1



DAY 7



Patient No: 015

Gender: Male, **Age** 18

Pyoderma localization: back skin.

DAY 1



DAY 7

