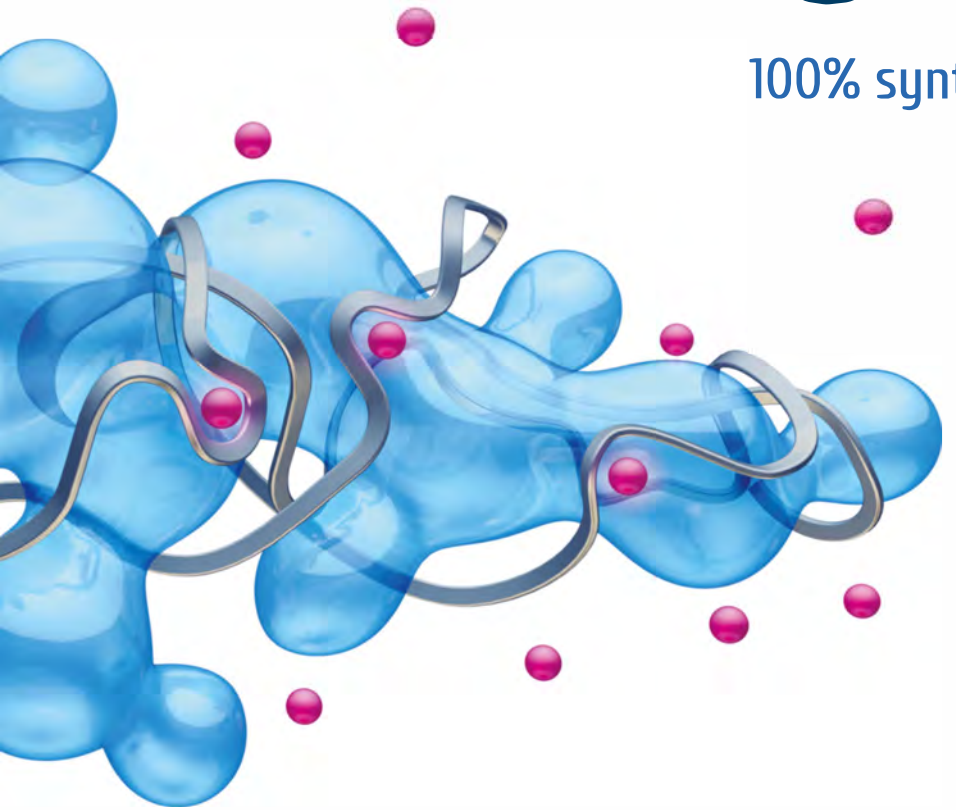
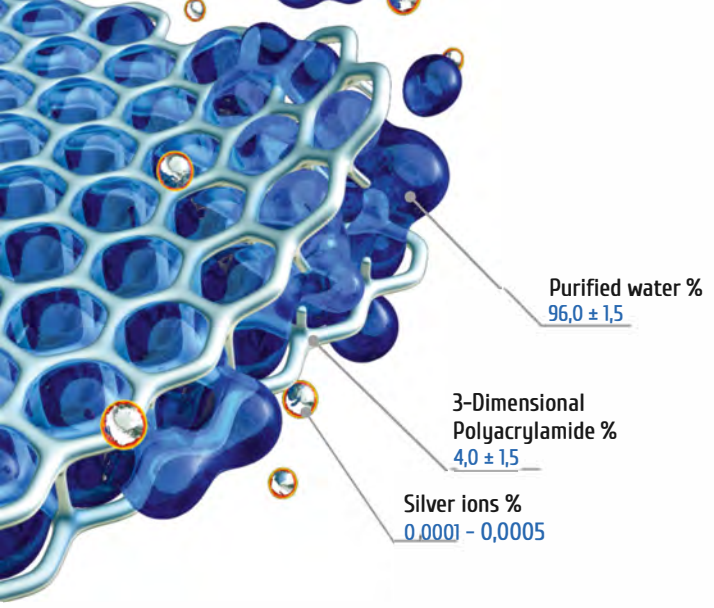
NOLTREX®

100% synthetic viscoprosthesis



- 14 clinical studies in the Russian Federation and CIS countries
- proven effect for up to 104 weeks



NOLTREX™ molecular weight > 10 000 000 Dalton

NOLTREX™ mechanism of action

- Restores the viscous properties of synovial fluid
- Reduced friction and mechanical stabilization due to high material density
- Hydrogel reduces stress on joint surfaces, helping to maintain cartilage integrity
- Relieves joint tissue irritation caused by friction
- Protects the implant from microbial contamination
- Is subjected to a long biodegradation process

NOLTREX™

100% synthetic viscoprosthesis

NOLTREX™ contains no animal-origin components

NOLTREX™ biocompatibility has been proved by *in vitro* (cell-rich fluid and cell cultures) and *in vivo* (rats, rabbits, dogs) methods

Both effectiveness and low price make NOLTREX™ the first choice of osteoarthrosis treatment product

NOLTREX™ is certified and actively used by physicians in Russia, CIS countries and South America.

Quality management system certified in accordance with ISO 13485: 2016

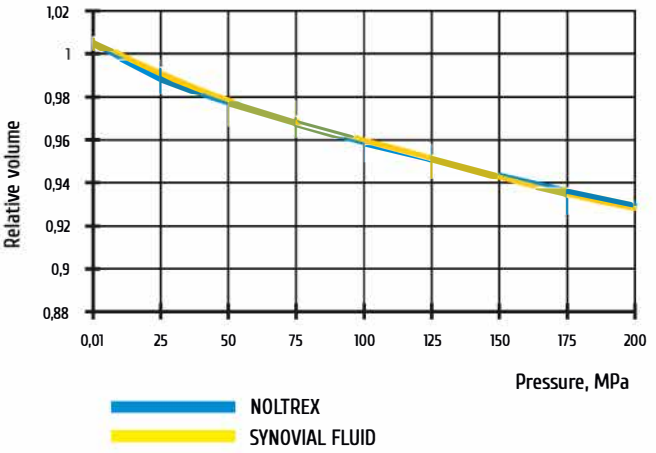
Global Sustainability Certification & Inspection Services

Studies showed that NOLTREX™ physical properties are identical to the natural properties of the synovial fluid in a healthy body. [1-3]

NOLTREX™ showed equal shockproofing parameters with normal synovial fluid in a wide range of external pressure.

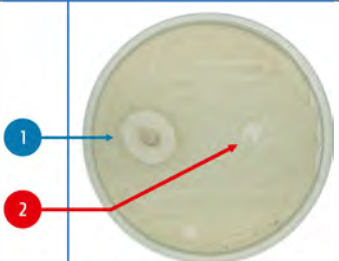
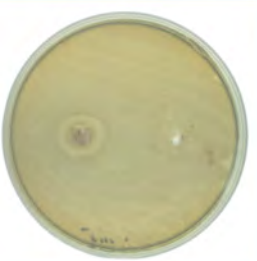
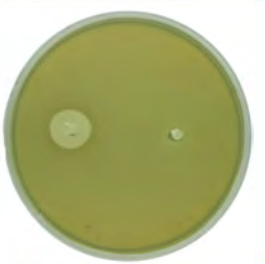
[1]Belonenko V.N. Role of bulk viscosity and acoustic parameters in tribological problems. Ultrasonic. 1991, v.29, 101-8.
[2]Zar V.V., Troitsky V.M., Stepanov A.I., Lopatin V. V. Future of viscoelastic behavior of 3-D structure of artificial and natural samples of articular liquids at the pressure 0.1-100 MPa // 16th International Conference of Chemical Thermodynamics. Russia, Suzdal, 01-06 july 2007. Vol.1.
[3]Lopatin V.V., Belonenko V.N., Zar V.V., Askadskii A.A.. Comprative study of mechanical behavior of human synovial fluid and polyacrylamide hydrogels depending on pressure.// Plastic masses. 2004 (7):24-29.

Viscosity properties of NOLTREX™ vs synovia at t = 37° C



Studies of NOLTREX™ antimicrobial properties confirm its bacteriostatic activity against different strains.

Polyacrylamide material with active silver ions in zone 1 inhibits bacterial growth compared to zone 2, which does not contain silver ions.

Bacteria strains used in test	S. aureus (MSSA) ATCC 25923	S. aureus (MRSA) ATCC 43300	E. coli ATCC 25922	P. aeruginosa ATCC 27853
				
Bacteriostasis zone, in mm	4,0	3,0	3,0	5,0

Histologically confirmed biocompatibility and ability to sustain joint tissues has been proven by experimental studies on animal models.

The study of NOLTREX™ influence on reparative chondrogenesis in the implantation test model of induced gonarthrosis[1]

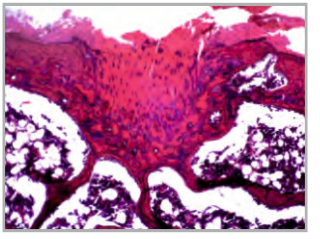
Animal Anatomy and Histology Department, K.I. Skryabin Moscow State Academy of Veterinary Medicine and Biotechnology, Moscow, Russia

Left knee joint: the hyaline cartilage wedge-shaped defect of the femoral epiphysis // Right joint: intact

Study group: injection of 0,2–0,3 ml of NOLTREX™.
Control group: injection of 0,2–0,3 ml of normal saline solution.
Terms of withdrawal from the study: day 0, 14, 30 of the experiment.

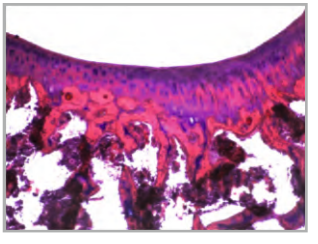
In the presence of NOLTREX™ in the cavity with damaged cartilage surface and impaired interactions between the cartilage and synovial cavity, through the optimization of tribological properties the favourable microclimate appears, promoting acceleration of reparative processes both in the cartilaginous and subchondrally located osseous tissue.

Osteoarthrosis animal model, Day 0

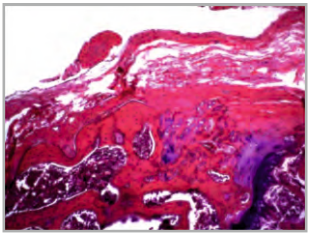


Condition of the hyaline cartilage, Day 14

Group received NOLTREX™

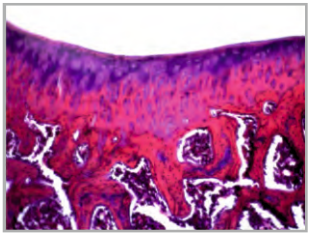


Control group

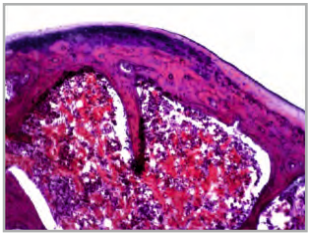


Condition of the hyaline cartilage, Day 30

Group received NOLTREX™



Control group



[1] Slesarenko N.A., Shirokova E.O. Reparative osseo- and chondrogenez in the conitions of induced osteoarthrosis in laboratory animals. Russian Veterinary Journal. 2012 (1): 6–8.
[2] Lopatin V.V., Askadskii A.A., Peregudov A.S., Berestnev V.A., Shekhter A.B. Structure and properties of polyacrylamide gels for medical applications. Polymer Science. Series A. 2004, vol. 46 (12): 1282–92.
[3] Shekhter A.B., Zar V.V., Voloshin V.P., Lopatin V.V. Tissue and cell reaction of the synovial media to intraarticular injection of polymer viscoprosthesis "NOLTREX" in experimental conditions. Almanac of Clinical Medicine. 2013, 28(7):20–24.

The study of NOLTREX™ effect on the condition of the knee joint in simple implantation test (in unaffected joint) [2,3]

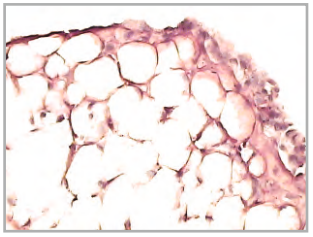
Laboratory of Pathomorphology, I.M. Sechenov Moscow Medical Academy, Moscow, Russia

Left jumping joint: 1,0 ml of NOLTREX™ was injected
Right joint (control): intact
Terms of withdrawal from the experiment: day 1, 3, 7, 14 and month 1, 3, 6 and 14 after the injection.

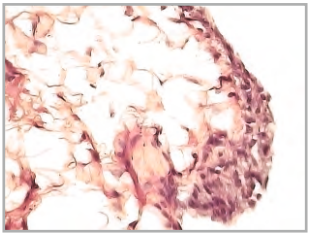
The histological study shows that intra-articular injection of NOLTREX™ doesn't lead to the development of synovitis and dystrophic process in the cartilage tissue. The material causes no allergic reactions, has a high grade of biocompatibility, doesn't embed into articular structures and sites over a long period of time in the cavity.

Condition of the synovial membrane of the experimental animals during study

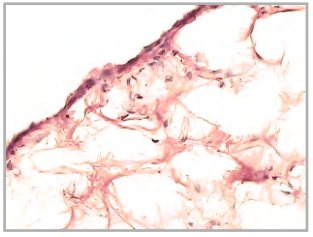
3rd Day after NOLTREX™ injection into the joint



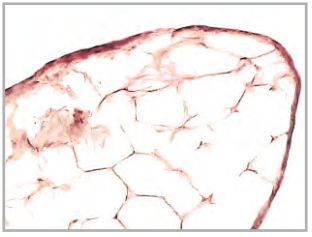
14th Day



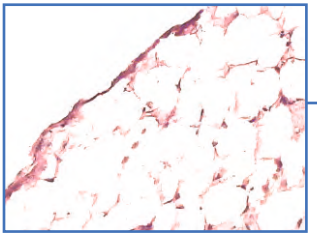
1st Month



6th Month



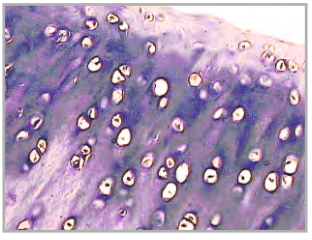
Intact joint during the whole period of study

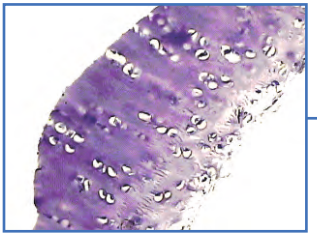


Condition of the hyaline cartilage of the experimental animals during study

7th Day after NOLTREX™ injection into the joint

6th Month





Prolonged and safe action of viscoprosthesis is ensured by absence in macroorganism of ferments decomposing polymer links. In experiment NOLTREX™ eliminates from the body within a several months by phagocytosis and noncellular lysis and excretes in the form of polyacrylamide oligomers without decomposing to acrylamide monomers.

Clinical trials of NOLTREX™

NOLTREX™ has been used in clinical practice since 2003.

Synthetic viscoprosthesis NOLTREX™ is recognized as a well-tolerated, safe and effective polymer material by patients with osteoarthritis of various large joints.

The average study duration was 6 months, but some authors performed much longer studies exceeding 2 years.

Two comparative (controlled) studies have been completed proving the significant effectiveness of local administration of NOLTREX™.

Currently, NOLTREX™ is used by orthopedic surgeons in osteoarthritis treatment for prosthetics of synovial fluid in humeral, cubital, radiocarpal, hip, knee and ankle joints.

In 2011 the **monotherapy with NOLTREX™** (i.e., one-time introduction during the course) was acknowledged as an effective way of palliative treatment of gonarthrosis.

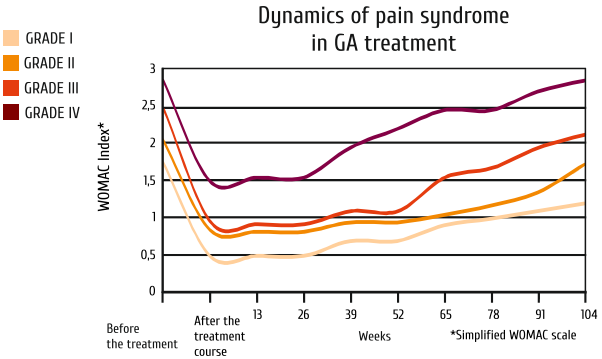
In the Traumatology and Orthopedics Clinic NOLTREX™ has been applied in patients after arthroplastic interventions on the knee joint and helped to reduce the post-operative rehabilitation period.

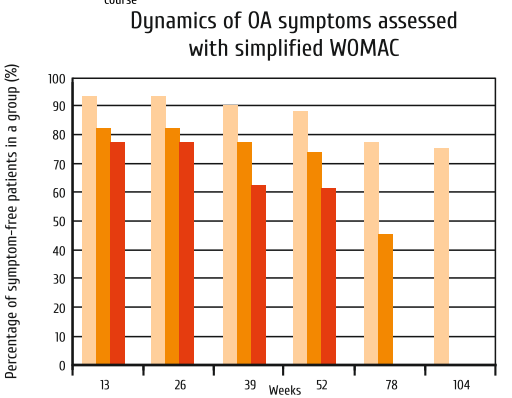
OA – Osteoarthrosis, NSAIDs – Nonsteroidal Anti-Inflammatory Drugs. Phase I – Phase I Clinical Trials, Phase II – Phase II Clinical Trials, MC – Multicentre studies, R – Randomized studies, NC – Noncontrolled (open) studies, C - Controlled studies.

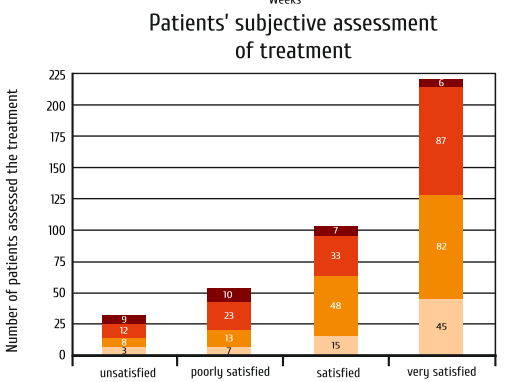
Studies (Medical institutions, authors, year)	Plan
Russian Scientific Research Institute of Traumatology & Orthopedics n.a. R.R. Vreden Emelyanov V.G., 2003	Phase I-II
Moscow Regional Scientific Research Clinical Institute n.a. M.F.Vladimirsky (MRSRCI) Buachidze O.Sh., Zar V.V., 2003	Phase I-II
Moscow Regional Hospital for War Veterans (MRHWV) Martynov D.V., 2003	Phase I-II
Peoples' Friendship University of Russia (PFUR) (Moscow Municipal Clinical Hospital No 13, MCH No 31) Zagorodniy N.V., 2003	Phase I-II
Ukrainian Medical Stomatological Academy (Ukraine, Poltava) Mokhnachyov O.V., Pelipenko V.P., 2007	Phase I-II
MRSRCI Buachidze O.Sh., Zar V.V., Tarek M., 2004	Phase I-II
Moscow Municipal Clinical Hospital No 59 Parakhin Yu.V., Popov F.V., Myakusheva T.N., 2009	Phase I-II
MRSRCI, PFUR, MRHWV Zagorodniy N.V., Zar V.V., 2006	Phase IIa MC, NC
Clinical Training Centre of the Semey State Medical Academy (Kazakhstan, Semey) Ivanova R.L., Agibaeva Zh.B., 2007	Phase IIb R, C
PFUR (MCH No 13, MCH No 31), MCH No 12 Zagorodniy N.V., Karpovich N.I., 2010	Phase IIa R, C
MRSRCI, MRHWV, Domodedovo Central District Hospital of Moscow region, Dzerzhinsky CDH MR, Ivanteevka CDH MR Zar V.V., Voloshin V.P., Martynov D.V., 2011	Phase IIb MC, NC

Number of patients	Number of injections	Duration	Results of the studies
10	3	6	Injection in patients with OA do not cause side effects, are well tolerated, sometimes a burning sensation occurs in the joint during the introduction of the material. Injections bring long lasting relief or disappearance of pain, as well as relief of dysfunction in the joint for about 6 months.
32	3	6,5	
18	3	6	
30	3	6,5	
67	3	7	
50	3	18,5	In 90% of patients with OA the effect lasts for 6 months. Efficiency after 6 month and 18,5 was in 88-95% and 67-85% cases respectively.
38	3-4	7	55% showed positive result after 2 injections, 26% after 3-4 injections. Prolonged effect for up to 6 month was observed in 76,3% of patients.
408	3	26	80% of patients with OA are satisfied with the treatment, 92% rate it positively. The synovitis occurred only in 0,5%, arthralgia – in 9,3% of cases. The duration of the effect depends upon the stage of OA (6 ÷ 12 months).
150	3	1,5	The patients with RA and OA received the following treatment: Xefocam, Ambene, Diprospan, NOLTREX™, control (a standard oral anti-inflammatory course). "Noltrex" provides local clinical response without systemic effects, other than those associated with the reduction of inflammation in the joint.
60	5	9	Control – NSAID intake. By the end of the study group "NOLTREX™ + NSAID" vs. Control, the last is higher in pain and lower in patient functional activity parameters.
186	1	6	"NOLTREX™" showed a tardive effect at 6 weeks. At 24 weeks after injection, the effect is not weakened and fixed.

Noltrex tolerability, duration and effectiveness study







Phase IIa noncontrolled (open) study

MRSRCI, PFUR, MRHWV (Zagorodny N.V., Zar V.V., 2006)[1]

- 527 patients with gonarthrosis aged 57,2 ± 7,3 years
- 408 patients completed the study (119 withdrawn)
- all patients received 3 injections of NOLTREX™ 2,5ml each with 6 day interval
- assessment before the treatment and at 0, 13, 26, 39, 52, 65, 78, 91 and 104 weeks after the 3rd injection
- to determine the clinical effect of NOLTREX™ the algofunctional assessment of simplified WOMAC questionnaire was used in the study (WOMAC Index maximum score is 3,0)

Conclusions:

- The tolerability and safety of the material-biopolymer was demonstrated in 527 patients with OA
- Significant benefits of NOLTREX™ application were achieved regardless of disease stage
- The duration of GA treatment effect was at least 52 weeks
- The adverse events were observed in the form of arthralgia and causalgia in 16% of cases, synovitis after the gel introduction was revealed in 2 patients (0,5%)
- Long-term efficacy of NOLTREX™ was proved, with neither local nor general iatrogenic complications peculiar to pharmaceutical agents intended for local (intra-articular) injections

[1] Zar V.V., Zagorodniy N.V., Martinov D.V. Effectiveness and safety of injectable endoprosthetics of sinovial fluid by cross-linked polimer NOLTREX for treatment OA knee. European Journal of Musculoskeletal Diseases. 2012, Vol.1 (1):23-32.

[2] Ivanova R.L., Omarbekova J.E., Agibaeva J.B. Modern treatment of osteoarthrosis (osteoarthritis) and secondary synovitis // Methodological Recommendations for General Practice Doctors, Clinical Resident Physicians and Interns. – Semipalatinsk, 2004. – 20 p.

Phase IIb controlled study

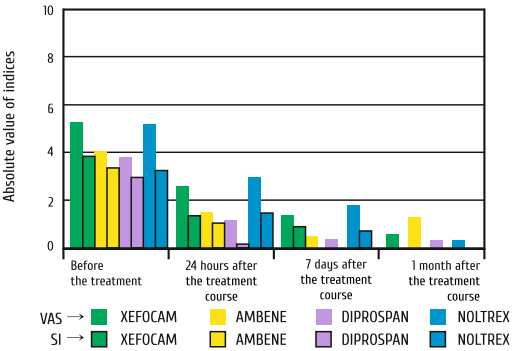
Clinical Training Centre of the Semey State Medical Academy
Kazakhstan, Semey (Ivanova R.L., Agibaeva Zh.B., 2007)[2]

- 76 patients with gonarthrosis aged 55,3 ± 3,1 years
- all patients completed the study
- the average duration of disease was 6,8 ± 3,2 years
- Group 1 – Xefocam, Group 2 – Ambene, Group 3 – Diprospan, Group 4 – **Xefocam/Diprospan + NOLTREX™**, Group 5 - control (standard anti-inflammatory course)
- assessment on 0, 1, 7 and 30 day after drug injection course or after the 3rd NOLTREX™ injection respectively
- treatment method with NOLTREX™: exudates evacuation if necessary, injection of Xefocam (or Diprospan), then after 1-3 days 3 weekly injections of NOLTREX™ 2,5ml each
- assessment of the results:
  - pain level on the VAS scale (0÷10), index of swelling in points (0÷4),
  - maximum walking speed measured in a 30-meter walk test in seconds,
  - GAG level in the blood serum according to Karyakina's method, in AU

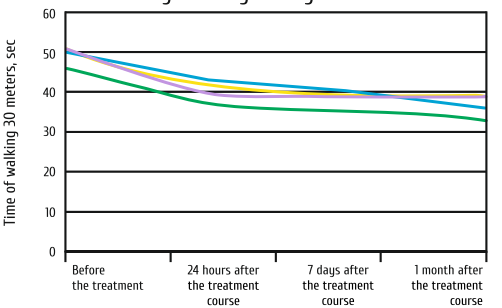
Conclusions:

- Effectiveness of NOLTREX™ was demonstrated at 20 patients with OA
- The prescription of NOLTREX™ in the absence of active synovitis allows to improve joint function
- NOLTREX™ provided a significant improvement in clinical parameters, as well as pronounced local clinical response with no systemic effects
- NOLTREX™ significantly reduces GAG serum level, which reflects its direct effect on reducing the destruction of cartilage through separating articular surfaces and cushioning
- Application of NOLTREX™ is recommended in combination with Diprospan or Xefocam, this scheme provides an improvement of functional condition, systemic inflammatory relief and protection of hyaline cartilage

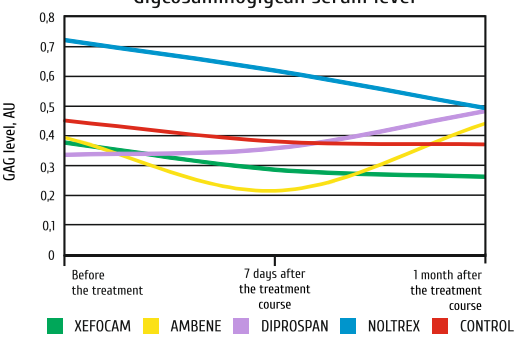
Dynamics of average values on the VAS scale and Swelling Index (SI) (p < 0,05)



Dynamics of the maximal 30-metre walking velocity during the treatment



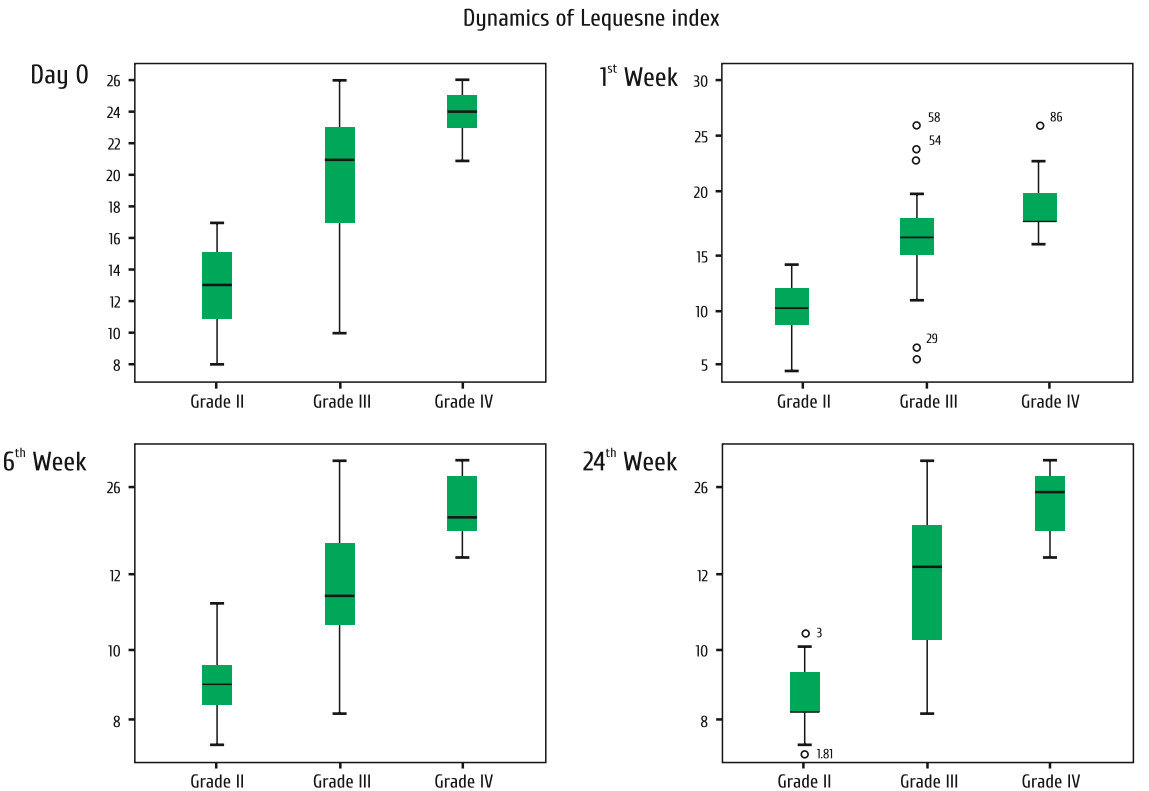
Glycosaminoglycan serum level

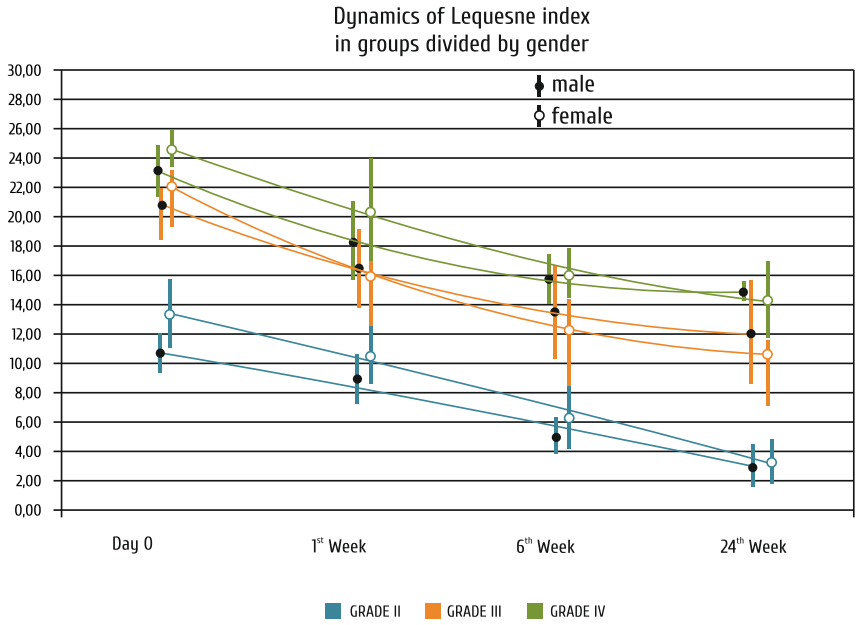


Phase IIb noncontrolled (open) study

MRSRCI, MRHWV, Domodedovo Central District Hospital of Moscow region, Dzerzhinsky CDH MR, Ivanteevka CDH MR (Zar V.V., Voloshin V.P., 2011) [1]

- 236 patients with gonarthrosis aged 65,3 ± 11,56 years
- 186 with uni- and bilaterial GA completed the study
- the ratio of II : III : IV grades in men and women was as follows 5,8 : 6,2 : 1 and 4,9 : 4,1 : 1 respectively
- treatment method - **monotherapy with NOLTREX™**: 5,0ml of NOLTREX™ as a single double-dosed injection
- assessment before the treatment and at 1, 6 and 24 weeks after single injection
- to determine effectiveness of NOLTREX™ the algofunctional assessment of Lequesne questionnaire was used





Conclusions:

- Intra-articular use of NOLTREX™ showed no development of either side effects or complications in 186 patients
- The injection is followed by rapid (within 1-6 weeks) improvement of the patient's physical activity; pain syndrome is decreased or stopped, significantly improving the patient's quality of life
- During study 23 patients abandoned their additional walking devices (cane or crutches)
- 24 weeks after injection the effect of NOLTREX™ is not only unflagging, but in most cases is fixed or becomes slightly more pronounced
- As a result of its prolonged functioning the isometric and dynamic capabilities of the lower limbs are improved due to unload of joints and muscles compensating lack of function

[1] Zar V.V., Voloshin V.P., Martynov M.D. Functional assessment of the results of intrajoint injection polyacrylamide gel "NOLTREX" in treatment of gonarthrosis patients. Almanac of Clinical Medicine. 2012, 27(12):18-24.

NOLTREX™ introduction technique

Recommendations of the Department of Traumathology & Orthopedics (PFUR, Moscow, Russia)

Noltrex™ should be injected into the joint cavity using needles 18Gx1½ and 21Gx1½ provided in a set with syringe. Application with needle 21Gx1½ decreases painfulness of injection, but requires greater pressure on a plunger and longer time of injection. 19Gx1½ Thin Wall needle is also reasonable.

If effusion is present in the joint it is advisable to stop exudation and introduce the material in 48-72 hours after the inflammation has stopped. Introduction of this material without preliminary evacuation of effusion is unadvisable.

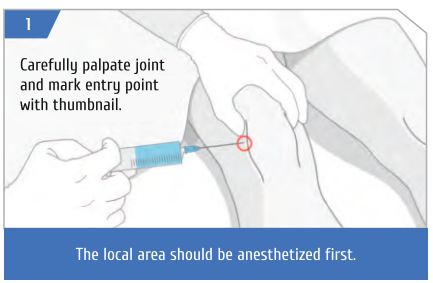
The material should be injected into the superior recess or under the patella, preferably on the outer side (the patient is in a lying position). To reduce pain during injection it is recommended to introduce Novocaine or Lidocaine (or another anesthetic at the physician's discretion) into the joint cavity and surrounding soft tissues as well.

When gel injected into the joint cavity the patient may experience filling in the joint, in case of accidental introduction into soft tissues - bursting sensation.

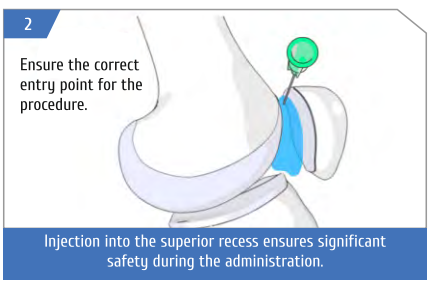
The average recommended time of injection is 3-5 minutes.

Accidental injection into soft tissues does not lead to intra-articular or soft-tissue complications. Nevertheless it is referred to undesired effects connected with noncompliance with the injection technique. Such event shall be eliminated by surgical evacuation or needle aspiration (if possible) of the material from soft tissues.

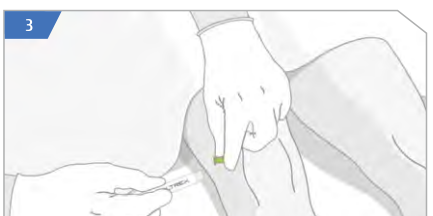
The load on the treated joint should be restricted for 24 hrs (or more if indicated).



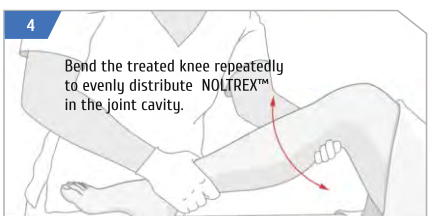
The local area should be anesthetized first.



Injection into the superior recess ensures significant safety during the administration.



Introduction of NOLTREX™ with 18Gx1½ needle is more convenient for a doctor but potentially is more dangerous for a patient.



After the injection several pendular movements are needed to accommodate even distribution of the material in the joint.

100% synthetic inert viscoprosthesis NOLTREX™ is a treatment of choice in palliative care of patients with osteoarthritis

DOSE NOLTREX™ INDIVIDUALLY

Recommended treatment method:

Joint type[7]	OA Grade	NOLTREX™ dosage schedules[1, 2, 3, 6]	Interval between the courses (month)[5]
Knee joint	I	2,5 ml	18 – 24
	II	2,5 ml → 2,5 ml, or 5,0 ml (2 syringes) at a time	12 – 18
	III	2,5 ml → 2,5 ml → 2,5 ml → 2,5 ml (as indicated)[4], or 5,0 ml (2 syringes) at a time, or 2,5 ml → 5,0 ml → 2,5 ml[4], or 5,0 ml → 2,5 ml → 2,5 ml[4]	6 – 12
	IV	2,5 ml → 2,5 ml → 2,5 ml → 2,5 ml → 2,5 ml[4], or 2,5 ml → 5,0 ml → 5,0 ml[4]	6 – 9
Hip joint	I	2,5 ml	18 – 24
	II	2,5 ml → 2,5 ml	12 – 18
	III	2,5 ml → 2,5 ml → 2,5 ml[4]	6 – 12
	IV	2,5 ml → 2,5 ml → 2,5 ml	6 – 9

Therapeutic decision. Commentaries:

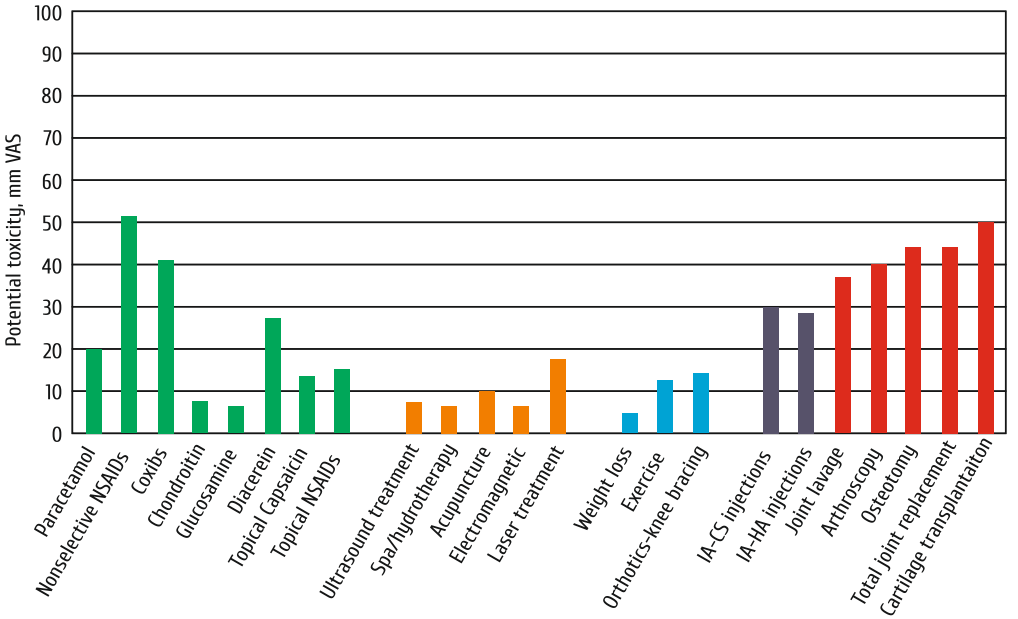
1) The recommended interval between multiple injections is one week (or more if indicated).
2) The treatment course is determined individually depending on the stage/severity of osteoarthritis and at the physician's discretion.
3) Multiple injections into the knee joint in a sitting position of patient through the anteromedial access increase the risk of damaging the articular cartilage and menisci with a large-diameter needle.
4) **Once the good clinical results are achieved, the treatment should be stopped prematurely to avoid overfilling the joint with dense, slowly resorbable material!**
5) It is recommended to repeat the course every 6-24 months depending on clinical results and/or symptomatic relapse.
6) A shorter repeated course of injections may be indicated
7) The material can be injected into other joints with a dose of 2.5 ml or less, depending on the joint size or internal resistance during injection.

Additional Information

Recommendations of the European League Against Rheumatism: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials[1]

- the first drug of choice for pain syndrome is Paracetamol
- corticosteroid intra-articular injections (IA-CS) determine short-term effect
- optimal gonarthrosis treatment plan is a combination of pharmacological and non-pharmacological (school of osteoarthritis for patients + exercise therapy + orthopaedic products + weight loss) methods
- toxicity profile for intra-articular injections of corticosteroids and HA is between the surgery and peroral NSAID course on one side, and paracetamol, chondroprotectors, diacerein, orthopedic devices and rehabilitation activities on the other
- effect size of intra articular injections of HA-products (IA-HA) is low

Toxicity profile of the gonarthrosis treatment modalities
(Jordan KM, Arden NK, Doherty M et al.)



Analysis of side effects of pharmaceutical products[2,3,4]

- nonselective NSAIDs carry the risks of gastropathy, peptic gastrointestinal ulcers
- selective NSAIDs (coxibs) during the prolonged administration, particularly in patients with impaired renal function, may lead to worsening of hypertension and increase the risk of cardiogenic complications by 33-60%
- propionic acid derivatives (Ibuprofen, Naproxen, etc.) increase the risk of acute coronary syndrome with non-ST elevation

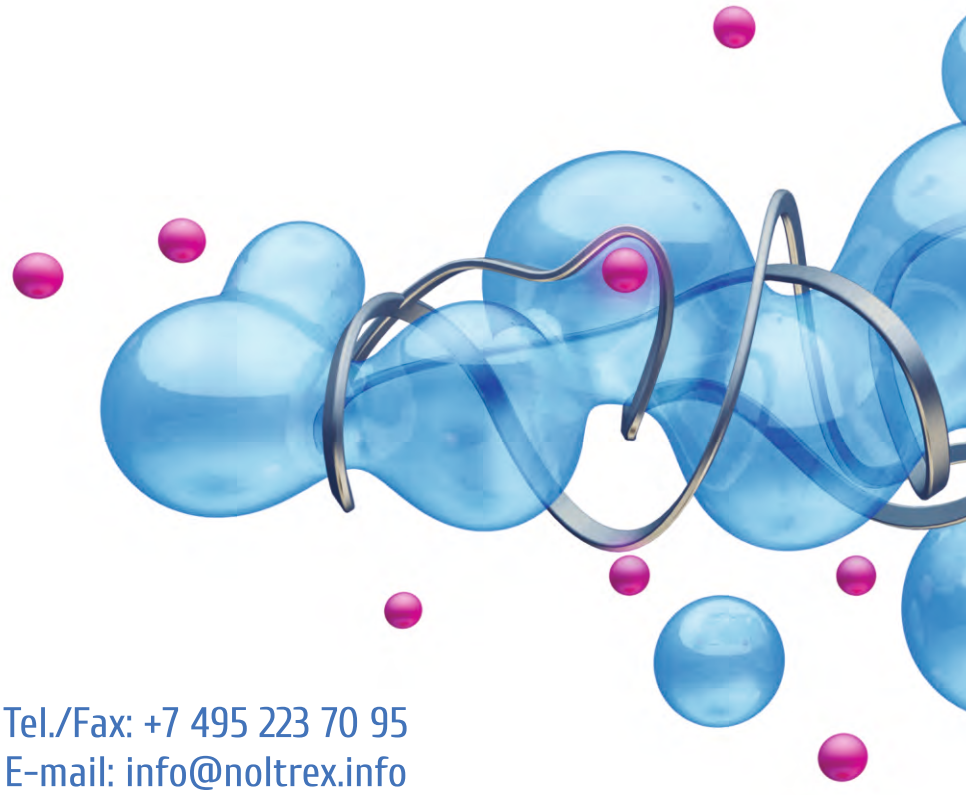
Cochrane Stroke Review Group[5]

- injections of HA-based products are effective for up to 13 weeks or less

Report of the Agency for Healthcare Research and Quality, US Department of Health and Human Services[6]

- HA-product intra articular injections, oral chondroprotectors, arthroscopic lavage or debridement showed uneven clinical effectiveness
- HA-product injections showed insignificant benefit as compared to placebo
- in USA viscosupplementation technique using HA-preparations was excluded from the list of medical services paid by the insurance companies as having no statistically proven effectiveness.

[1] Jordan KM, Arden NK et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis. 2003, Dec; 62 (12):1145-55.
[2] Bello AE. DUEXIS(®) (ibuprofen 800 mg, famotidine 26.6 mg): a new approach to gastroprotection for patients with chronic pain and inflammation who require treatment with a nonsteroidal anti-inflammatory drug. Ther Adv Musculoskelet Dis. 2012 Oct; 4 (5):327-39.
[3] Johnson AJ. et al. The cyclo-oxygenase-2 inhibitor celecoxib perturbs intracellular calcium by inhibiting endoplasmic reticulum Ca2+-ATPases: a plausible link with its anti-tumour effect and cardiovascular risks. Biochem J. 2002 Sep 15; 366(Pt 3):831-7.
[4] Grimaldi-Bensouda L et al. Risk of ST versus non-ST elevation myocardial infarction associated with non-steroidal anti-inflammatory drugs. Heart. 2011 Nov; 97(22):1834-40. Epub 2011, Aug 31.
[5] Bellamy N, Campbell J. et al. Viscosupplementation for the treatment of osteoarthritis of the knee (Review). The Cochrane Library 2008, Issue 1.
[6] Samson DJ et al. Treatment of primary and secondary osteoarthritis of the knee. Evid Rep Technol Assess (Full Rep), AHRQ Publication No. 07-E012. 2007, Sept; 157:1-157.



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