Individual immunotherapy

An information brochure on the alternative and causal treatment of autoimmune diseases

Patient information

Content

01 | Overview of the individual immunotherapy

A proven therapy alternative for autoimmune diseases

Autoimmune diseases can occur in a wide variety of forms. This is caused by an immune reaction against the body's own structures due to an imbalance in the immune system.

The endogenous and exogenous factors that lead to an autoimmune disease are as diverse as the symptoms. Targeted treatment for those affected is just as complex and difficult.

Individual immunotherapy uses the patient-specific immune response to the individual immune processes. A personalised immunotherapeutic agent is produced from the body's own material, thus reflecting the entire complexity of the personal immune response. The disease-dependent endotype is determined. The immunomodulatory effect of the individual immunotherapeutic agents can thus address the actual cause of the disease.

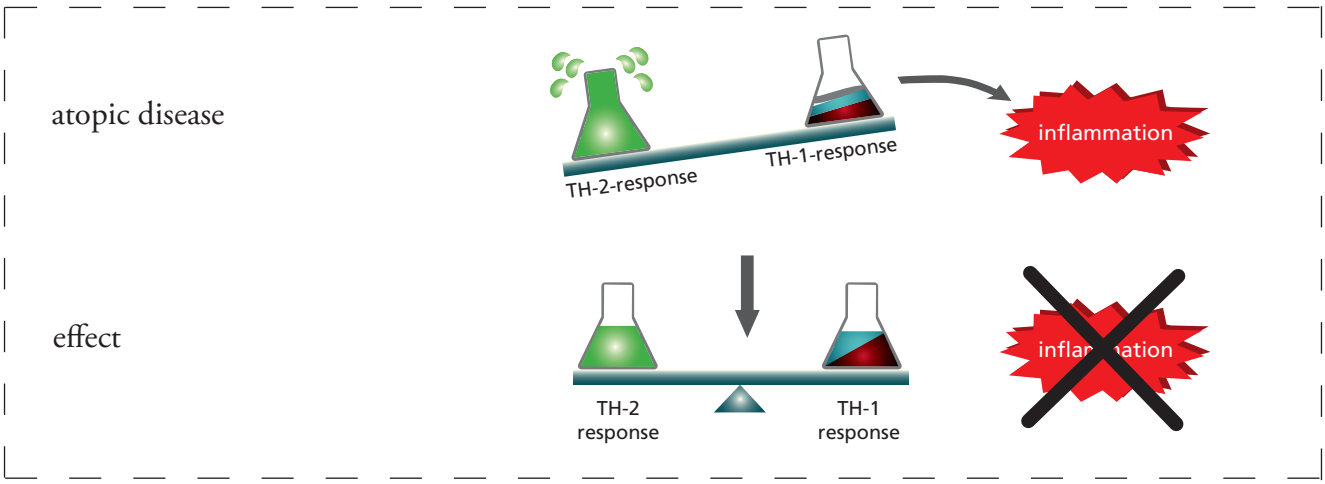

Figure 1: Possible effect of the individual immunotherapy

Advantages of the individual immunotherapy

01 causal therapeutic approach
no purely symptomatic treatment

02 from the body's own material
free of cortisone

03 long-lasting therapeutic successes
even after the therapy ends

04 very good tolerance
can be used from infancy onwards

05 use of patient-specific immunological components

06 personalised production according to age and severity of the disease

02 | Individual immunotherapy in detail

Scientific background and possible mechanism of action

In recent years, a steady increase in illnesses has been observed, which are caused by a malfunction of the immune system. A strong overreaction of the immune system to endogenous and exogenous factors often manifests itself in the form of an autoimmune disease, e.g. an atopy. This can affect a wide variety of organs (see Fig. 2).

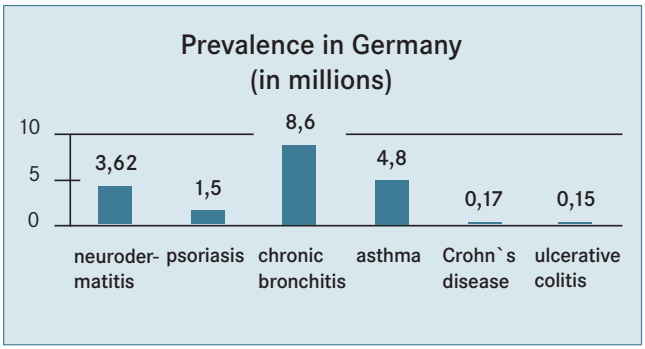

Figure 2: Prevalence of various autoimmune diseases in Germany. Source: Guidelines for the relevant disease

An atopy is often caused by a change in the response of certain T helper cells. The resulting imbalance of the immune system leads to inflammation, which often takes a chronic course (see Fig. 3).

Modern medicine has not yet managed to treat atopic diseases efficiently. Symptomatic therapies are nearly exclusively used, some of which have no long-term success and can be accompanied by significant side effects.

To produce FBM-PHARMA GmbH's individual immunotherapeutic agents, the immunoactive components of the patient's own material (blood and urine) are used. They model the disease-dependent complexity of the immune process and can thus develop their highly specific immunomodulatory effect.

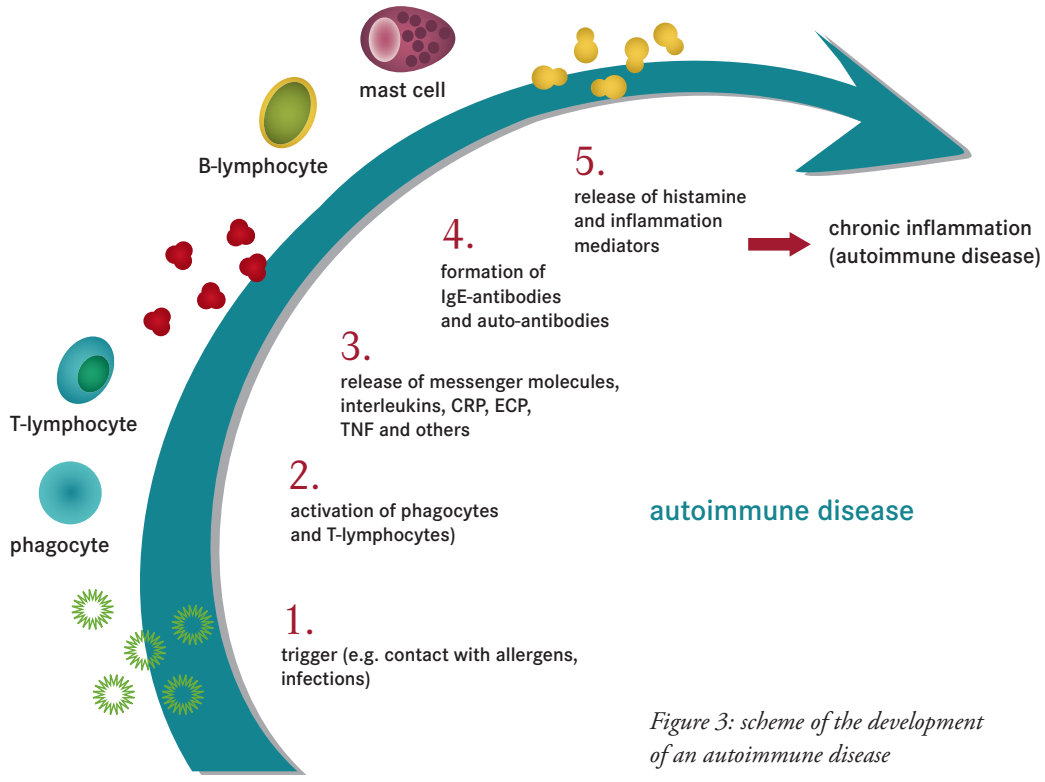

Figure 3: scheme of the development of an autoimmune disease

Mechanisms of action using urexent® as an example

In the past, measurable physiological parameters of the immune system have been shown to change in atopic patients. IgE-class antibodies directed against immunogenic substances are produced in significantly higher amounts. The number of eosinophils also increases. The cause of the overreaction is now assumed to be an imbalance in the activity of different T helper cell types (amplification of the Th2 response) and this leads to an inflammatory reaction.

The immunomodulatory effect of the individual immunotherapy - in addition to the external effects such as improvement in complexion, reduced itching - has an influence on the formation of certain immunoactive substances.
This can result in an amplification of the Th1 response and thus restore the immune system's balance (see Fig. 4).

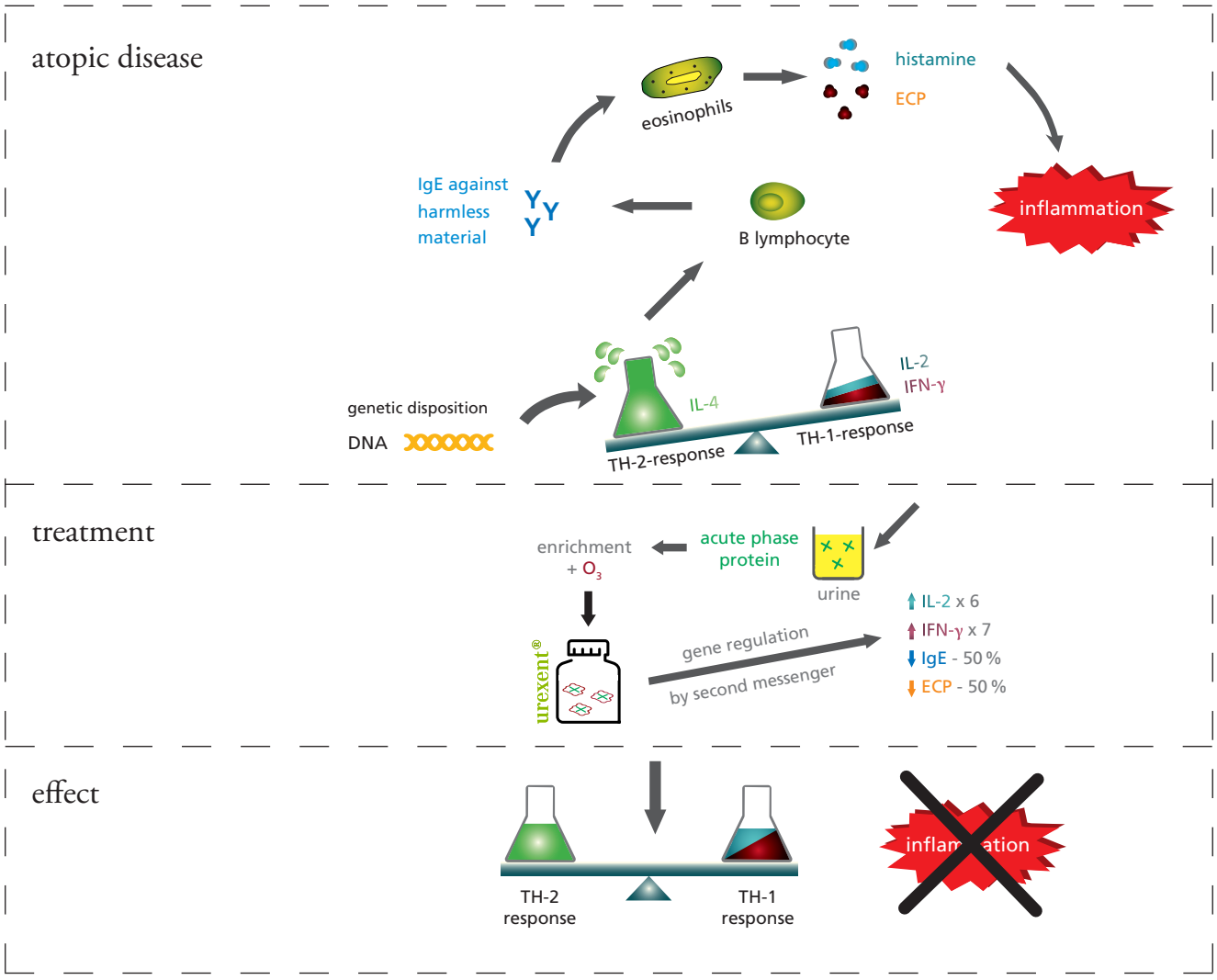

Figure 4: Possible mechanisms of action of our individual immunotherapeutic agents using urexent® as an example

Th1/Th2 balance

It is known from literature that in neurodermatitis, for example, the activity of type 2 T helper cells (Th2) predominates[1,2,3] and the activity of type 1 T helper cells (Th1) is reduced. This excessive activation of Th2 leads to an increased production of IgE antibodies and inflammatory mediators such as histamine and ECP (Eosinophilic Cationic Protein).

In order to correct this pathological condition, the balance between Th1 and Th2 should be restored. urexent® seems to have a positive influence on this balance, as initial blood tests in patients showed a 50% reduction in IgE and ECP and a 6-fold and 7-fold increase in interleukin-2 and interferon-gamma (increased activity of Th1), respectively[5].

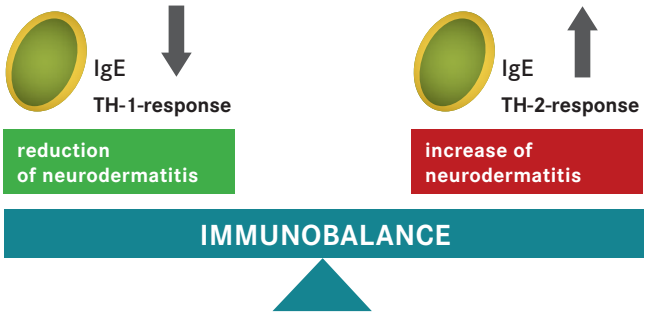

Figure 5: Schematic representation of the immune balance in atopic diseases

Anti-antibody production

Another effect cited in the description of the mode of action of immunomodulating substances is the formation of antibodies. This "network theory" by Niels Jerne (Nobel Prize for Medicine 1984) states that the body forms its own antibodies (ab) against those antibodies that are currently involved in an immune response and thus down-regulate their increased formation (negative feedback). It is conceivable that the processing and ozonisation of the patient's urine could split proteins and demask possible epitopes. After oral intake of urexent®, these processed proteins could be recognised as "foreign" and stimulate the production of the body's own anti-ab, which then intercept the excessively produced IgE ab and subsequently normalise the immune response.

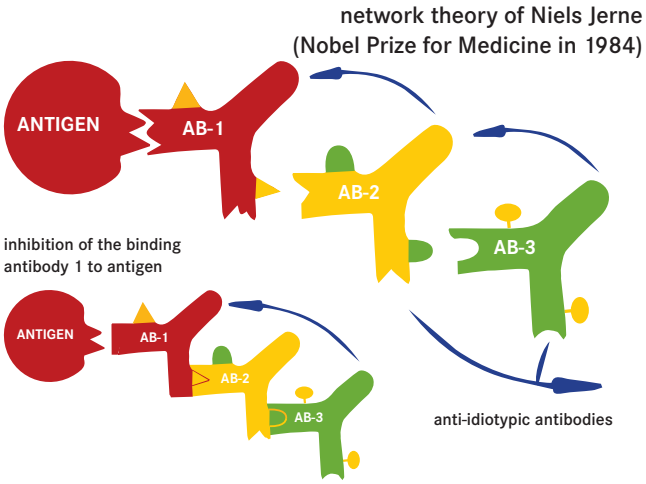

Figure 6: Network theory by Niels Jerne. Negative feedback of an antibody mediated immune response

Oxidatively modified proteins

The third possible effect of urexent® could be the ozonisation of the patient's urine. Recent findings show that the body produces ozone even with a normal physiological immune response[7,8]. The researchers describe that this endogenous ozone subsequently oxidises a wide variety of mediators, which in turn stimulate the formation of antioxidative enzymes and can apparently activate up to 230 different genes via specific effector molecules. It is now believed that a mild oxidative stress in the body can regulate or normalise a high oxidative stress (e.g. caused by neurodermatitis).[6]

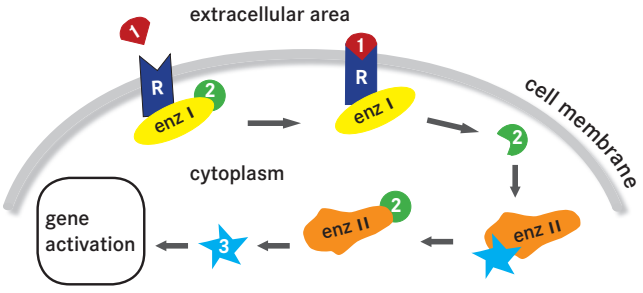

Figure 7: Signal transduction by oxidatively modified effector molecules (1) leads to gene activation via the release of intracellular signal molecules (2,3), enz = enzyme

All three possible modes of action of urexent® described above underline the causal therapeutic approach. It stands to reason that these mechanisms of action are transferable to blood and blood plasma preparations.

03 | Individual immunotherapeutic agents of FBM-PHARMA GmbH

Therapy options for the treatment of autoimmune diseases

The basis for our individual immunotherapeutic agents are the following patient's own body substances:

- Whole blood
- Blood plasma
- Urine (urexent®)

- **Immunotherapeutic agents based on the patient's own blood**

Our individual immunotherapeutic agents based on the patient's own blood are administered as combination preparations in the form of syringes for subcutaneous injection and drops for oral administration. The patient can administer the treatment at home.

Depending on the age or severity of the disease, the blood preparation can also be produced as a pure drop preparation. Our whole blood preparations are particularly suitable for moderate to severe forms of an autoimmune disease.

- **Immunotherapeutic agents based on the patient's own blood plasma**

Our products based on the patient's own blood plasma can be produced as a drop preparation alone or as a combination preparation (subcutaneous injections and drops).

Plasma preparations are particularly suitable for mild to moderate diseases.

- **Immunotherapeutic agents based on the patient's own urine (urexent®)**

Our immunotherapeutic agent urexent®, a drop preparation based on the patient's own urine, is a completely non-invasive therapy option.

urexent® is therefore particularly suitable for babies and toddlers as well as for adolescents and adults with a mild form of autoimmune disease.

Therapy options based on experience with previous prescriptions of our individual immunotherapeutic agents

severity of the disease	age of the patient	immunotherapeutic agents
severe-moderate	adult	blood (combi)*
severe-moderate	adolescent	blood (oral*)
moderate -mild	adult	blood plasma combi*
moderate -mild	adolescent	blood plasma (oral*)
moderate-mild	infant/child	urexent® (oral*)
mild	adult/adolescent	urexent adult® (oral*)

*(„combi" = subcutaneous injection and oral drops / „oral" = pure drop preparation)

Figure 8: The above figure does not represent a fixed allocation, but serves only as a general orientation.

In specific individual cases, the therapist of course chooses the appropriate immunotherapeutic agent (e.g. in an adolescent with a very severe form of the disease, the therapist can use a blood preparation (injection and drops) as therapy).

04 | Therapy success with individual immunotherapeutic agents

Results of urexent® treatment on patients with neurodermatitis

In many diseases, the effectiveness of the therapy depends on whether the cause of the disease can be eliminated. Only then is lasting relief from the symptoms possible.

In the case of atopic diseases such as neurodermatitis, some of those affected have suffered over a long period of time. Many conventional therapies treat only the symptoms and often achieve only a temporary effect, but no long-term improvement in the symptoms.

Individual immunotherapy, on the other hand, focuses on the cause of the disease and has achieved considerable success in the past.

The results are summarised in recent random sample surveys carried out during treatment with urexent® (see Fig. 9 and 10). In 73% of those affected, a clear improvement in their health was observed in the first 6 months of treatment. This response increased to 85% after 12 months of therapy.

This includes those patients who achieved complete or partial remission, which is described as lasting for up to 4 years. Patients who have grown older and were treated with urexent® now report that their skin has been free of symptoms for more than 10 years.

In addition to the visible improvement in skin complexion, the immunomodulating effect of urexent® was investigated. ELISA tests were used to measure the levels of certain immunoactive substances. In the case of neurodermatitis, it was possible to increase the reduced levels of interferon-γ and interleukin-2, which strengthened the response of type 1 T helper cells. At the same time, the concentration of IgE and ECP decreased, i.e. the response of type 2 T helper cells decreased (see also Fig. 4). Overall, this can lead to a state that is close to normal physiological values.

The complex interplay of the endogenous and exogenous factors that cause neurodermatitis, such as genetic predisposition, stress, food and detergent additives and environmental pollution, causes an individual immune system reaction in each patient.

The use of endogenous, patient- and disease-dependent substances that are just as individual as the disease itself is exactly what is taken into account when using the body's own materials. This results in the superiority of individual immunotherapy over other forms of therapy.

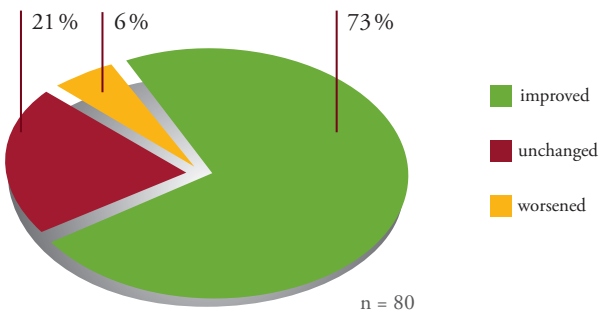

Figure 9: Treatment success in patients suffering from neurodermatitis approx. 6 months after starting urexent® therapy

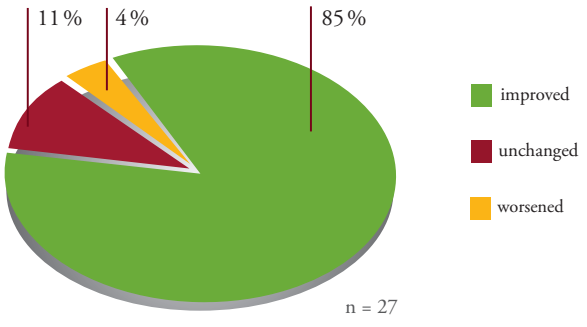

Figure 10: State of health of patients suffering from neurodermatitis up to 4 years after completion of urexent® therapy

05 | FBM-PHARMA GmbH

Your partner for individual immunotherapy for autoimmune diseases

FBM-PHARMA GmbH is a medium-sized pharmaceutical company based in Ludwigshafen, Germany, and specialises in the individual production of biological drugs based on the patient's own blood and urine. Our products focus on the treatment of chronic inflammatory immune diseases (autoimmune diseases).

- Inflammation of the skin
  (e. g. psoriasis, neurodermatitis, eczema)
- ammatory respiratory diseases
  (e. g. COPD, pulmonary fibrosis,
  bronchial asthma)
- Inflammation of the gastrointestinal tract
  (e. g. Crohn's disease, ulcerative colitis)
- as adjuvant therapy for malignant diseases

Based on our previous experience, the treatment is almost free of side effects due to the use of the body's own substances. Individual immunotherapy based on the patient's own urine can thus be used from infancy onwards.

The individual immunotherapeutic agents are free of steroids such as cortisone and free of synthetic ingredients. They offer a useful therapy option for the youngest patients in particular.

Due to the exclusive manual production of the individual immunotherapeutic agents, it is possible to produce an individually tailored magistral preparation for each patient.

The production of the personalised immunotherapeutic agents in our clean rooms is carried out in a controlled environment according to pharmaceutical standards subject to the guidelines of the Medicinal Products Act, the AMWHV (Decree for the Manufacture of Medicinal Products and Active Pharmaceutical Ingredients) as well as the current GMP guidelines under regulatory supervision.

An EU manufacturing authorisation and FBM-PHARMA GmbH's GMP certificate guarantee production in accordance with the strictest hygiene requirements, thus ensuring a high-quality immunotherapeutic agent that is manufactured specifically for each patient.

indivdiualized medicine - targeted and well tolerated

01 the starting material is the patient's own blood and/or urine	**04** logistical processes coordinated by FBM-PHARMA
02 very good tolerance with almost no side effects	**05** delivery to the patient's local pharmacy
03 free of cortisone and synthetic ingredients	**06** application at home

06 | Production of individual immunotherapeutic agents

Pharmaceutical production and logistics

According to the AMG (German Pharmaceuticals Act), blood collection is defined as an active part of producing drugs. Therefore, our blood preparations can only be commissioned by specially trained therapists, who cooperate with FBM-PHARMA GmbH and have been approved by the authorities. For urine preparations (urexent®), the procedure is simplified and requires no explicit approval by the authorities.

After being diagnosed by the supervising therapist, the patient provides a sample of his/her blood or urine in the affiliated practice. It is then transported to FBM-PHARMA GmbH's production plant by a logistics specialist. Individual production takes - depending on the product - 2 to 4 weeks. FBM-PHARMA GmbH coordinates the logistical processes.

07 | Use of individual immunotherapeutic agents

Dosage and duration of treatment for an autoimmune disease

The personalised immunotherapeutic agents are administered in ascending concentration levels. The gradual increase in the daily dose and the concentration of active ingredients enables the body to gently adapt to the drug

This applies to both oral drop preparations and injectables. In this way, the effective concentration of the processed immunoactive substances from blood and urine is continuously increased over the course of the therapy, up to the maximum concentration.

Proven dosage schemes are available for each preparation, which ensure correct use and are described in detail in the instructions for use.

An additional dosing schedule enables the respective daily dose to be recorded.

drop preparation
dosage plan / month

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day	date	dilution	number of drops		remarks
			morning	evening	
01					
02					
03					
04					
05					

Figure 11: Example of a dosing schedule for a drop preparation

[1] Ji H, Li XK: Oxidative Stress in Atopic Dermatitis. In: Oxid Med Cell Longev.2016; 2016:2721469.doi:10.1155/2016/2721469. Epub 2016 Feb 23.
[2] Kapp A.: The role of eosinophilic granulocytes for the pathogenesis of atopic dermatitis /neurodermatitis. Eosinophilic products as markers of disease activity. In: Hautarzt. 1993 Jul;44(7):432-6.
[3] Czarnowicki T, et al.: Early pediatric atopic dermatitis shows only a cutaneous lymphocyte antigen (CLA)(+) TH2/TH1 cell imbalance, whereas adults acquire CLA(+) TH22/TC22 cell subsets. In: J Allergy Clin Immunol. 2015 Oct;136(4):941-951.e3. doi: 10.1016/j.jaci.2015.05.049. Epub 2015 Aug 1
[4] Eigene Erhebung durch FBM-PHARMA.
[5] FBM-PHARMA, data on file (Messungen durchgeführt an der Uni Heidelberg, mittels ELISA-Test).
[6] Zanardi I, Borrelli E, Valacchi G, Travagli V, Bocci V.: Ozone: A Multifaceted Molecule with Unexpected Therapeutic Activity. In: Curr Med Chem. 2016;23(4):304-14.
[7] Babior BM, Takeuchi C, Ruedi J, Gutierrez A, Wentworth P Jr.: Investigating antibody-catalyzed ozone generation by human neutrophils. In: Proc Natl Acad Sci U S A. 2003 Mar 18;100(6):3031-4. Epub 2003 Feb 24.
[8] Wentworth P Jr., et al.: Evidence for Antibody-Catalyzed Ozone Formation in Bacterial Killing and Inflammation. In: Science. 13 Dec 2002:Vol. 298, Issue 5601, pp. 2195-2199,DOI: 10.1126/science.1077642.

* The mechanisms and modes of action described in this document are derived mechanisms based on the findings of scientific literature and empirical medicine.

If you have any questions, the FBM-PHARMA GmbH team, as a specialist in individual immunotherapy, will be happy to assist you or put you in contact with an FBM-PHARMA GmbH-affiliated therapist.

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