Micro-immunotherapy
The immunotherapy for daily clinical practice

This brochure is for doctors and other health professionals only
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1. Introduction

The correct functioning of the immune system is the basis of good health. The immune system acts as a protective shield against pathogens and helps maintaining the integrity of the organism. It is also responsible for restoring the internal balance (homeostasis) after a challenge and preventing attacking the body’s own tissues.

Multiple factors can alter immune homeostasis and favour the onset or progression of diseases. In fact, a large number of the disorders affecting the world population today are linked to immune dysfunctions.

Why then is the immune system not a central part of all diagnostic and therapeutic approaches? And of any preventive measure?

Assessing the patient’s immune status, analysing the factors that affect it and restoring immune balance are essential in daily clinical practice.

Immunotherapy currently offers a wide range of possibilities to specifically regulate the immune system. Among them, micro-immunotherapy is a therapeutic approach that uses immunomodulatory substances, such as cytokines, in low doses. In this way, the physiological processes of the body are mimicked and a well-tolerated treatment is ensured.

Due to their characteristics, micro-immunotherapy formulas can safely be used for all age groups, are compatible with other treatments and can be integrated into any therapeutic strategy.

This leaflet describes the properties of micro-immunotherapy and the specificities of the formulas currently used in daily clinical practice.
2. The immune system as central part of an integrative approach

2.1 The immune system: guardian of health

The immune system is a network of organs, cells and molecules that actively defends the body from external aggressors (e.g. pathogens, toxins) and internal disruptive factors (e.g. mutated or cancer cells). This defence function is executed by activating an immunoinflammatory response.\textsuperscript{1,2}

At the same time, the immune system has to avoid attacking the body’s own tissues, commensal bacteria and other harmless substances (e.g. allergens, nutrients), in order to maintain balance in the body and to prevent autoimmunity. This function is known as regulation or tolerance.\textsuperscript{1,2}

Signalling molecules, such as cytokines, play a decisive role in maintaining the balance between these two functions, which is also called immune homeostasis (Figure 1). A multitude of pathologies are associated with alterations in cytokine concentrations.\textsuperscript{3}

\textit{Figure 1: Immune homeostasis: a dynamic balance between two functions}

\textbf{Health depends on immune homeostasis.}
There are multiple factors that can alter immune homeostasis and favour the development or progression of disease (Figure 2). Examples include infections, particularly chronic ones (such as herpesvirus infections), an unbalanced diet, physical inactivity, obesity, intestinal dysbiosis, chronic stress, sleeping disorders or environmental contamination.

Therefore, in order to maintain and/or restore long-term health, it is important to assess the status of the patient’s immune system, determine the individual factors that affect its function and treat the encountered imbalances.

**Figure 2: Links between immune dysregulation and pathology**

Virtually all diseases are linked to imbalances of the immune system.
2.2 Immunomodulation with micro-immunotherapy

Immunotherapy is based on the treatment or prevention of diseases by targeting the immune system. Among the current approaches in immunotherapy, micro-immunotherapy (low dose immunotherapy) is characterized by using immunomodulatory substances, such as cytokines, in low doses, thereby mimicking physiological processes and improving treatment tolerability\(^5\).

Micro-immunotherapy speaks the same language as the body: it uses the same molecules that naturally coordinate the response of immune cells and other components.

This therapeutic approach has a broad scope of applications and is aimed at:

- Maintaining or restoring immune homeostasis
- Neutralizing the pathological effects of immune stressors (e.g. viral infections)
- Counteracting the development or progression of pathologies related to an immune imbalance

In the 70s, the Belgian doctor Maurice Jenaer was one of the pioneers in micro-immunotherapy\(^6\). At present, micro-immunotherapy formulas are recommended in daily clinical practice on an international level.
3. Micro-immunotherapy

3.1. Immunomodulatory substances

Cytokines are the messenger molecules used naturally by the immune system to mediate the communication between its different components and, thus, coordinate and regulate its response, both on a local and systemic level. In fact, altered cytokine expression is associated with excessive, aberrant or deficient immune reactions in the body. Different types of cytokines are described in Table 1.

Table 1: Different types of cytokines and their main functions

<table>
<thead>
<tr>
<th>Type</th>
<th>Main functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukins (IL-1, IL-2, IL-6, IL-10, etc.)</td>
<td>Regulation of cell proliferation and differentiation, immune activation/suppression</td>
</tr>
<tr>
<td>Interferons (IFN-α, β, γ, etc.)</td>
<td>Regulation of the innate immune response, antiviral and antiproliferative action</td>
</tr>
<tr>
<td>Chemokines (MIP-1ß, IL-8, RANTES, etc.)</td>
<td>Control of cell migration, recruitment and adhesion</td>
</tr>
<tr>
<td>Tumor necrosis factors (TNF-α, TNF-β)</td>
<td>Modulation of inflammatory and immune responses</td>
</tr>
<tr>
<td>Transforming growth factors (TGF-β, BMPs, etc.)</td>
<td>Regulation of the immune system (immunomodulation) and maintenance of tissue homeostasis</td>
</tr>
<tr>
<td>Haematopoietins (G-CSF, GM-CSF, EPO, etc.)</td>
<td>Stimulation of cell proliferation and differentiation</td>
</tr>
</tbody>
</table>

At present, new cytokines and new cytokine functions are continuously being discovered. It is an ever-expanding field.

Micro-immunotherapy uses cytokines and, therefore, speaks the same language as the immune system.
3.2. Low doses

Cytokines are highly active substances with strong effects on the body. This is why they circulate in the organism in very low concentrations ranging from nanograms ($10^{-9}$g), picograms ($10^{-12}$g) to femtograms ($10^{-15}$g). In fact, the serum levels of many of the cytokines in healthy individuals are in the picomolar range$^{8,9}$.

In clinical research, an increasing tendency towards reducing the doses of active substances of immunological origin can be observed$^{10-12}$. The aim is to ensure the efficacy of the treatment, while avoiding the toxicity associated with the use of these substances in doses that are relatively too high. Micro-immunotherapy uses low doses (LD) and ultra-low doses (ULD), as it takes into account the natural functioning of the immune system, making it a unique and innovative approach within immunotherapy.

Thanks to the use of low doses, micro-immunotherapy constitutes a gentle immunotherapy.

4. Specificities of micro-immunotherapy formulas

Within the field of micro-immunotherapy, the formulas that are used today in clinical practice, whose efficacy and good safety profile have been validated in multiple studies$^{13-18}$, have the following characteristics:

- They are mainly composed of cytokines, which play a key role in the communication and regulation of the immune system.
- These substances are administered in low doses, that is, doses similar to or lower than physiological concentrations in order to respect the natural functioning of the immune system.
- They have four other particularities that make them more specific and targeted, since they take into account other key properties of the immune system.
The specificities of micro-immunotherapy formulas are detailed below. The first of these particularities is their action on the overall system with multiple objectives.

4.1. Action on the overall system with multiple objectives

It is well known that multiple mediators are implicated in the coordination of the immune response. They act synergistically to induce local and/or systemic responses. In fact, the immune reaction is determined by the simultaneous presence or absence of different cytokines in the microenvironment – it is said to be context-dependent.\(^\text{3,19}\).

In order to respect the immune system’s complexity, micro-immunotherapy formulas are composed of a specific combination of active substances in low and ultra-low doses (LD & ULD).\(^\text{14-18}\).

The specific combination of the active substances of each formula and their preparation mode are selected according to:

- Their implication in the pathophysiology of the disease
- Their interaction with the other substances contained in the formula
- The reaction that is meant to be induced in the body

\(^1\) The substances contained in the micro-immunotherapy formulas are prepared following a specific manufacturing process called “Serial Kinetic Process (SKP)”, which consists of a serial dilution process of 1:100 followed by vertical shaking and repeated a defined number of times.\(^\text{14-18}\).
The objective of each active substance within a specific formula may be different, depending on its preparation mode, the interaction with the rest of the substances and the sequence (Figure 3).

![Ultra-low doses](30C) ![Low doses](10C) ![1C]

<table>
<thead>
<tr>
<th>30C</th>
<th>10C</th>
<th>1C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Downregulation...</strong></td>
<td><strong>Maintenance...</strong></td>
<td><strong>Upregulation ...</strong></td>
</tr>
</tbody>
</table>

...of the biological activity of the substance in the body

*Figure 3: Objectives of the active substances used in micro-immunotherapy formulas according to their preparation mode, interaction and sequence*

A simple example: in case of acute inflammation it can be beneficial to downregulate the action of IL-1 – a proinflammatory cytokine – by using it in ULD. Whereas in case of an immune deficiency, the goal would be to upregulate its action by using it in LD to support the immune response.

These reverse effects of interleukins, growth factors and other immunomodulatory substances, depending on the applied dose, have been described in various studies. Today, the effects of LD can be explained by the biological phenomenon known as Hormesis, or biphasic dose-response curve, which is well established in the literature. In the case of ULD, the mechanism of action is not entirely understood, although there is extensive clinical experience, as well as experimental evidence of their downregulatory effects. A recent publication suggests that the presence of submicron particles (150-1000nm) could induce a hormetic response. However, there is more research required in this field.

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*Hormesis refers to a phenomenon whereby the same substance can exert stimulating and/or beneficial effects at low doses and inhibitory and/or toxic effects at high doses. This phenomenon was first observed in the field of toxicology, leading to the formulation of the Arndt-Schulz law. At present, hormesis is defined as an adaptive response of biological systems to moderate stimuli, through which the system optimizes its functionality and becomes more resistant to stronger challenges.*
Example: formula ARTH

The formula ARTH is used in clinical practice for acute, subacute, and chronic inflammation\textsuperscript{iii}.

In case of osteoarthritis, the objectives of the formula ARTH are to downregulate the biological activity of different substances (Figure 4).

![Active substances within the formula ARTH and sequential immunoregulatory objectives](image)

**Figure 4: Active substances within the formula ARTH and sequential immunoregulatory objectives**

Micro-immunotherapy formulas are specifically designed to act on the overall system with multiple objectives.

\textsuperscript{iii} Based on the clinical practice and experience of doctors from the international micro-immunotherapy associations (AEMI, IFMi and MeGeMIT).
Recent *in vitro* and *in vivo* studies have shown the anti-inflammatory effect of the medicine 2LARTH®. For instance, a study from 2020 conducted in a murine model of rheumatoid arthritis has revealed a decrease in plasma levels of TNF-α and a reduction of clinical signs of arthritis (reduction of edema and cartilage loss) after treatment with micro-immunotherapy in comparison to placebo (Figures 5a, 5b and 5c).
4.2. Sequential signalling

The immune response is characterized by a fine-regulated set of events that develop over time\textsuperscript{24}. For example, when a pathogen crosses the physical and chemical barriers of the body (e.g. skin, secretions), the innate immune response is activated. If the innate system fails to eliminate the pathogen, further cells will join in, and the more specialized mechanisms of the adaptive immune response will intervene (Figure 6).

Furthermore, both the innate and the adaptive immune response can be subdivided into different stages that follow in chronological order: first the antigen recognition takes place, then further cells are activated and recruited. Subsequently, neutralisation or elimination of the foreign element is set in motion, and finally homeostasis is restored, all coordinated through regulatory processes (Figure 6).

\textbf{Figure 6: Stages of the immune response to an initial infection}
Micro-immunotherapy formulas reproduce this chronobiological sequence of events. That’s why they are taken in a certain order to transfer sets of information to the body in succession.

The formulas are available in capsules packed in blister packs and numbered from 1 to 10 (Figure 7). Each capsule has a specific distribution of cytokines and other mediators in LD and ULD, which are supposed to be taken strictly in order.

Thus, the constant repetition of the sequence over time is aimed to enable the immune system to regain and sustain its own capacity for self-regulation.

Figure 7: Sequential intake of micro-immunotherapy formulas

Micro-immunotherapy formulas are administered sequentially in order to mimic the chain of events of the immune response.
4.3. Sublingual administration

The sublingual mucosa has several characteristics that make it particularly attractive as a route for the administration of pharmaceutical active substances. Firstly, its histological features (thin epithelium, non-keratinized structure) confer it a high permeability. Secondly, its immunological characteristics (local presence of immunocompetent cells, relatively low number of inflammatory cells) ensure its immune competence and a low risk of systemic adverse reactions\textsuperscript{25-27}.

These particularities of the sublingual mucosa offer numerous pharmacological benefits (Figure 8).

Figure 8: Features of sublingual mucosa and benefits associated to the administration via this route
Micro-immunotherapy formulas are taken sublingually due to the numerous benefits derived from the particular characteristics of the mucosa in the oral cavity. The treatment is contained in capsules, the content of which is poured under the tongue where the granules slowly dissolve (Figure 9). Micro-immunotherapy formulas are preferably taken in the morning on an empty stomach, 15 or 30 minutes before a meal or 1 hour after.

1. Micro-immunotherapy treatments follow a specific sequence (marked visually on the blister with numbers from 1 to 10). Take one of the capsules respecting the order.

2. Open the capsule.

3. Pour the granules contained in the capsule under the tongue, where they slowly dissolve.

*Figure 9: Sublingual intake of micro-immunotherapy formulas*

Sublingual administration is an effective and safe route in immunotherapy and provides multiple benefits to patients.
4.4. Nucleic acids

Along with immune messengers (cytokines), micro-immunotherapy formulas used in daily clinical practice also contain nucleic acids (DNA and RNA) and specific nucleic acids (SNAs) in ultra-low doses.

DNA and RNA

From an immunological perspective, nucleic acids are substances with antigenic properties, meaning that they are capable of influencing the immune response. Added to micro-immunotherapy formulas, these molecules act to some extent as inducers of an “alarm state” within the immune system, thereby stimulating the immune response, without overactivating it.

SNAs

Micro-immunotherapy formulas also contain another type of nucleic acids, the specific nucleic acids (SNAs). These are small synthetic oligonucleotides aimed at preventing the synthesis of a certain protein involved in the pathological process to be treated. For example, in the case of a virus, which is composed of proteins and genome, blocking the synthesis of one or more essential proteins of the virus makes it no longer viable.
5. Fields of application

Micro-immunotherapy formulas can be used in all patients with immune dysregulation. There are a variety of formulas within the field of micro-immunotherapy. The choice of the appropriate treatment depends on the detected immune imbalance, the pathology to be treated and the symptoms of the patient. Given that alterations of the immune system are related to a wide range of diseases, micro-immunotherapy formulas have a broad spectrum of applications (Table 2).

Table 2: Main fields of application of micro-immunotherapy formulas

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Viral infections and reactivations</td>
<td></td>
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<tr>
<td>Bacterial infections</td>
<td></td>
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<tr>
<td>Allergies</td>
<td></td>
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<tr>
<td>Autoimmune diseases</td>
<td></td>
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<tr>
<td>Stress-related disorders and depression</td>
<td></td>
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<tr>
<td>Bone and joint disorders</td>
<td></td>
</tr>
<tr>
<td>Neurodegenerative diseases</td>
<td></td>
</tr>
<tr>
<td>Dental diseases</td>
<td></td>
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<tr>
<td>Complementary cancer treatment</td>
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</tbody>
</table>

Likewise, more and more veterinary professionals highlight the good results of micro-immunotherapy formulas in domestic animals.
6. Summary

Micro-immunotherapy is an immunotherapy aimed at recovering and/or sustaining immune competence in the long term.

It uses immunomodulatory substances like cytokines in low doses, in order to mimic the body’s physiology and avoid unwanted side effects in patients. Micro-immunotherapy formulas currently used in daily clinical practice have four further characteristics that make them more specific and targeted (Table 3).

Table 3: Features of micro-immunotherapy formulas

<table>
<thead>
<tr>
<th>Basic features</th>
<th>Specific features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunomodulatory substances</td>
<td>Action on the overall system with multiple objectives</td>
</tr>
<tr>
<td>Low doses</td>
<td>Sequential signalling</td>
</tr>
<tr>
<td>Sublingual administration</td>
<td></td>
</tr>
<tr>
<td>Nucleic acids</td>
<td></td>
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</tbody>
</table>
Micro-immunotherapy formulas communicate with the immune system in its own language, without replacing it or blocking its functions to achieve both local and systemic action in a physiological, sequential and coordinated manner (Figure 10).

**Figure 10: Summary of the mode of action of micro-immunotherapy formulas**

Children, adults and the elderly can use them since they have a good safety profile and are easy to take sublingually. They are compatible with other therapeutic approaches and can be integrated into any treatment and/or prevention plan (Figure 11).

**Figure 11: Benefits of micro-immunotherapy formulas**

Micro-immunotherapy is an immunotherapy that can easily be integrated into the daily clinical practice, with the aim to regulate the patient’s immune system in a gentle, tailored and sustainable way.


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