

# LL-37

## Overview

LL-37 is a human antimicrobial peptide derived from the precursor protein hCAP-18, belonging to the cathelicidin family. It plays a crucial role in the innate immune system by exhibiting broad-spectrum antimicrobial activity against bacteria, viruses, and fungi. LL-37 is produced by various cells, including neutrophils, macrophages, and epithelial cells, and is present in tissues such as the skin, respiratory tract, and gastrointestinal tract.

## Potential Benefits

LL-37, as a multifunctional antimicrobial peptide, offers various potential health benefits due to its wide-ranging physiological and immunological effects. These benefits make it a promising candidate for therapeutic applications in several areas of health and disease management:

### 1. Enhanced Immune Defense

- LL-37 kills a broad spectrum of pathogens, including bacteria, viruses, and fungi.
- Helps prevent and manage infections, particularly those resistant to antibiotics.
- Disrupts biofilms, which are protective layers formed by bacteria, aiding in the treatment of chronic infections.

### 2. Improved Wound Healing

- LL-37 promotes keratinocyte migration and proliferation, accelerating skin repair.
- Stimulates angiogenesis (new blood vessel formation) to enhance tissue regeneration.
- Effective in managing chronic wounds, diabetic ulcers, and burns.

### 3. Anti-Inflammatory and Immunomodulatory Effects

- LL-37 reduces excessive inflammation, protecting against tissue damage.
- Modulates cytokine release, contributing to a more controlled immune response in inflammatory conditions.

### 4. Gut Health

- Supports gut barrier integrity, preventing "leaky gut" and inflammation.
- Protects against gastrointestinal infections by targeting harmful bacteria while supporting beneficial microbiota.
- Could have applications in managing inflammatory bowel disease (IBD).

### 5. Skin Health

- Plays a critical role in defending against pathogens in the skin.

- Dysregulation in LL-37 has been associated with conditions like rosacea, psoriasis, and atopic dermatitis, suggesting its therapeutic potential.
- Improves skin barrier function, aiding in eczema and other skin barrier disorders.

## 6. Cancer Prevention and Therapy

- LL-37 can suppress tumor growth in certain cancers by activating immune responses.
- It enhances apoptosis (programmed cell death) of malignant cells in some contexts.
- However, in specific cancers, it might promote growth, necessitating careful therapeutic targeting.

## 7. Prevention and Management of Chronic Infections

- Effective against persistent biofilm-related infections, including those associated with medical devices and chronic wounds.
- May help treat conditions like urinary tract infections (UTIs) and cystic fibrosis-associated lung infections.

## 8. Respiratory Health

- Protects the respiratory tract from bacterial and viral infections.
- Potential role in managing conditions like pneumonia, bronchitis, and even influenza.

## 9. Neuroprotective Effects

- Preliminary studies suggest LL-37 may help reduce inflammation in neurodegenerative diseases like Alzheimer's and Parkinson's disease.
- Protects against the harmful effects of chronic systemic inflammation on the brain.

## 10. Cardiovascular Health

- By reducing systemic inflammation, LL-37 may lower the risk of atherosclerosis and cardiovascular diseases.

## 11. Vaccine and Therapeutic Adjuvant

- LL-37 has been studied as an adjuvant to boost vaccine efficacy by enhancing immune activation.
- It could improve responses to vaccines for bacterial and viral infections.

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## Potential Side Effects/Safety

### 1. Excessive Inflammation

- While LL-37 can modulate inflammation positively, excessive levels may amplify pro-inflammatory cytokines like IL-6 and TNF- $\alpha$ .
- This can exacerbate inflammatory conditions, such as psoriasis or rheumatoid arthritis.

### 2. Autoimmune Reactions

- In some autoimmune diseases, LL-37 may act as an autoantigen, triggering immune responses against the body's own tissues.

- For example, in **systemic lupus erythematosus (SLE)**, LL-37 has been found to bind DNA and form immune complexes that drive disease progression.

### 3. Cancer Promotion

While LL-37 may suppress tumors in certain contexts, it can also promote cancer cell proliferation, angiogenesis, and metastasis in others (e.g., breast, ovarian, and lung cancers).

Its role in cancer is context-dependent, necessitating careful targeting and monitoring.

### 4. Cytotoxicity

- High concentrations of LL-37 can disrupt not only microbial membranes but also host cell membranes, leading to cytotoxic effects.
- This may cause damage to healthy tissues, particularly in sensitive areas like the lungs or gastrointestinal tract.

### 5. Allergic Reactions

- LL-37 may induce allergic or hypersensitivity reactions in some individuals, particularly if administered as a therapy without adequate testing for immune compatibility.

### 6. Dysbiosis

- LL-37's antimicrobial activity, while beneficial against pathogens, may disrupt the balance of the gut or skin microbiome.
- This could lead to **dysbiosis**, causing secondary infections, inflammation, or impaired barrier function.

### 7. Potential Resistance Development

- Overuse or improper use of LL-37-based treatments may lead to microbial resistance or evasion strategies, such as altered membrane compositions in bacteria.

### 8. Off-Target Effects

- LL-37 interacts with a variety of receptors and signaling pathways, such as Toll-like receptors (TLRs), which could lead to off-target effects.
- This might manifest as systemic inflammation or unintended activation of immune pathways.

### 9. Worsening of Chronic Conditions

- Overproduction of LL-37 has been implicated in these conditions, where it contributes to excessive inflammation and exacerbates symptoms.

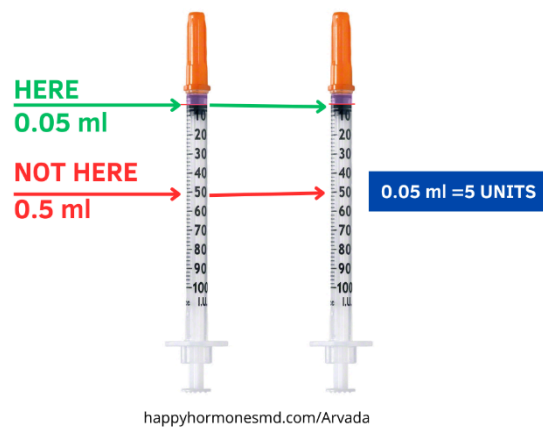
### 10. Considerations for Therapeutic Use

- **Dose-Dependent Effects:** LL-37's effects vary widely based on its concentration. High doses may cause toxicity, while low doses may not be effective.
- **Route of Administration:** Systemic administration poses higher risks of off-target effects and immune system activation compared to localized applications (e.g., topical use).

- **Individual Variability:** Genetic and environmental factors influence how individuals respond to LL-37, affecting both efficacy and risk of side effects.
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### Dosing Guidelines

- **Topical Application (Not currently available):** Clinical studies have explored LL-37 for wound healing. In a phase 2b clinical trial involving patients with venous leg ulcers, LL-37 was applied topically at concentrations of 0.5 mg/mL and 1.6 mg/mL. The treatment was administered twice weekly for four weeks, resulting in significant healing improvements, particularly in patients with larger ulcers.
- **Subcutaneous Injection: 0.1mg (0.05ml or 5 units) daily**, with treatment durations ranging from two to four weeks.



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### Cost

LL-37 is currently only available as a research peptide. Please see document titled “Research Peptide Information” in the Education Folder under Records in the patient portal.

**LL-37 5mg Vial (2mg/ml):** \$148.50 (Includes shipping and bacteriostatic water for reconstitution). 1 vial = 50 doses.

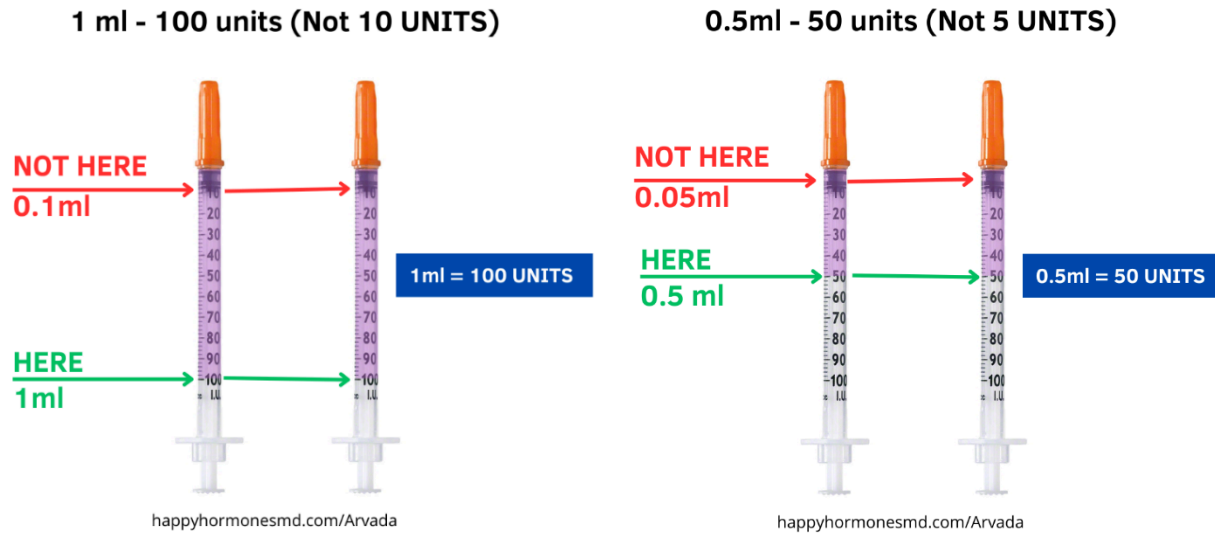
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### Reconstitution Instructions

#### IMPORTANT:

- Follow the instructions below regarding the amount of bacteriostatic water to use when reconstituting the peptide. **DO NOT** follow the instructions that come with the peptide.
- Do **NOT** throw away the vial of bacteriostatic water!!! It is a multiuse vial and can be used for your next order!

**LL-37 5mg Vial (2mg/ml):** Inject **2.5 ml of bacteriostatic water** into the vial (**2.5ml = 250 units**). You will need to inject 2 full 1ml syringes and one 0.5ml syringe of water into the vial.



- See the **document** titled *“Reconstituting Medications in Powder Form”* in the Education Folder in the patient portal.
- See the following Instructional **videos** in the Education Folder in the patient portal:
  - *“Reconstituting Powdered Medications”*
  - *“Injection Video – Introduction”*
  - *“Injection Video – Drawing Up the Medication”*
  - *“Injection Video – Administering the Medication”*

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### Storage and Stability

- Vials are shipped as **lyophilized powder**, requiring no refrigeration during shipping.
- In Lyophilized Form:
  - Stable for up to 3 years in the freezer and 2 years in the refrigerator.
  - Protect from light.
- Once Reconstituted:

- Stable for 6 weeks.
  - Must be refrigerated and kept away from light.
  - Avoid placing vials in the refrigerator door to prevent degradation from frequent temperature changes.
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### Important Disclosures

- The statements in this document have not been evaluated by the US Food and Drug Administration (FDA).
  - These products are not intended to diagnose, treat, cure, or prevent any disease.
  - Compounded medications and research peptides are not FDA-approved.
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### Quality Assurance

- All peptides undergo extensive third-party testing with publicly available Certificates of Analysis (COA).
- Testing includes:
  - RP-HPLC (Reversed-Phase High-Performance Liquid Chromatography)
  - Mass Spectrometry (MS)
  - Sterility testing
  - Additional assessments meeting or exceeding U.S. Pharmacopeia (USP) and USP-National Formulary (NF) standards.

The manufacturer ensures safety, quality, and efficacy to comply with regulatory mandates.

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