UROMUNE®
PERLINGUAL SPRAY

Bacterial immunomodulator

Perlingual Spray Immunotherapy

Inactivated Whole Bacteria

More Comfortable Application

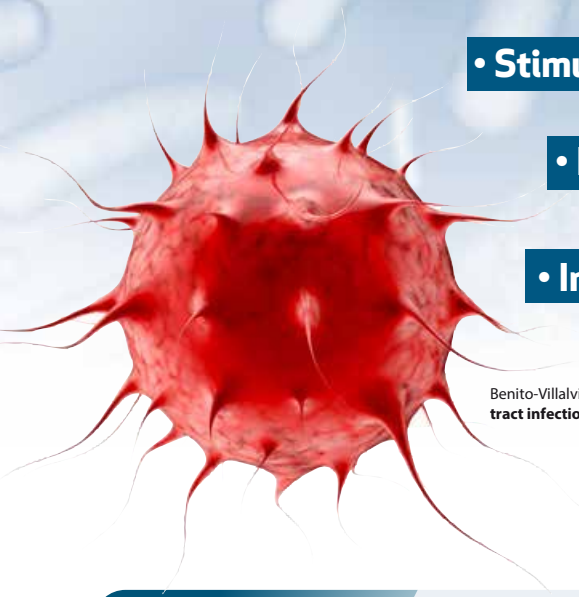
INNOVATING
AND SHARING
IDEAS

Since 1992

inmunotek
alergia e inmunología

UROMUNE® PERLINGUAL SPRAY

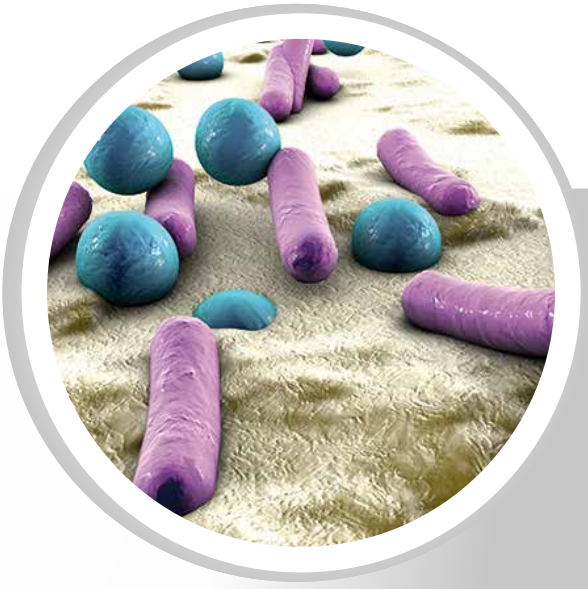
SPRAY BACTERIAL IMMUNOMODULATORS



- **Stimulate activity** of dendritic cells
- **Increase** production of **cytokines**
- **Increase** the proliferative response of **CD4 lymphocytes**

Benito-Villalvilla C, *et al*. **Immunological mechanisms activated by a polyvalent bacterial preparation used for the treatment of recurrent urinary tract infections (RUTIs)**. Allergy 2016; 71(S102):118–272.

SPRAY INACTIVATED WHOLE BACTERIA



- **High antigenic potential** because it contains components capable of activating the **Immune System**
- **Wide spectrum** of action since it stimulates the immune system **by increasing the response** even in microorganisms not contained in the vaccine
- **High security** because it has no capability to infect

Hessle *et al*. **Gram-Positive bacteria are potent inducers of monocytic Interleukin-12 (IL-12) while Gram-Negative bacteria preferentially stimulate IL-10 production**. Infection and Immunity, June 2000; 68(6):3581-3586

Lorenzo-Gómez *et al*. **Comparison of sublingual therapeutic vaccine with antibiotics for the prophylaxis of recurrent urinary track infection**. Front. Cell. Infect. Microbiol. 5:50. doi: 10.3389/fcimb.2015.00050.

SPRAY WHOLE BACTERIA *vs* BACTERIAL LYSATES

ADVANTAGES

- Optimun process of inactivation of **whole bacteria conserve capacity of immune system response**
- **Essential components** for the immune system activation **are present in whole bacteria**
- **Whole bacteria** have **higher capacity to activate the immune system** than bacterial lysates

Hessle *et al*. **Gram-Positive bacteria are potent inducers of monocytic Interleukin-12 (IL-12) while Gram-Negative bacteria preferentially stimulate IL-10 production**. Infection and Immunity, June 2000; 68(6):3581-3586

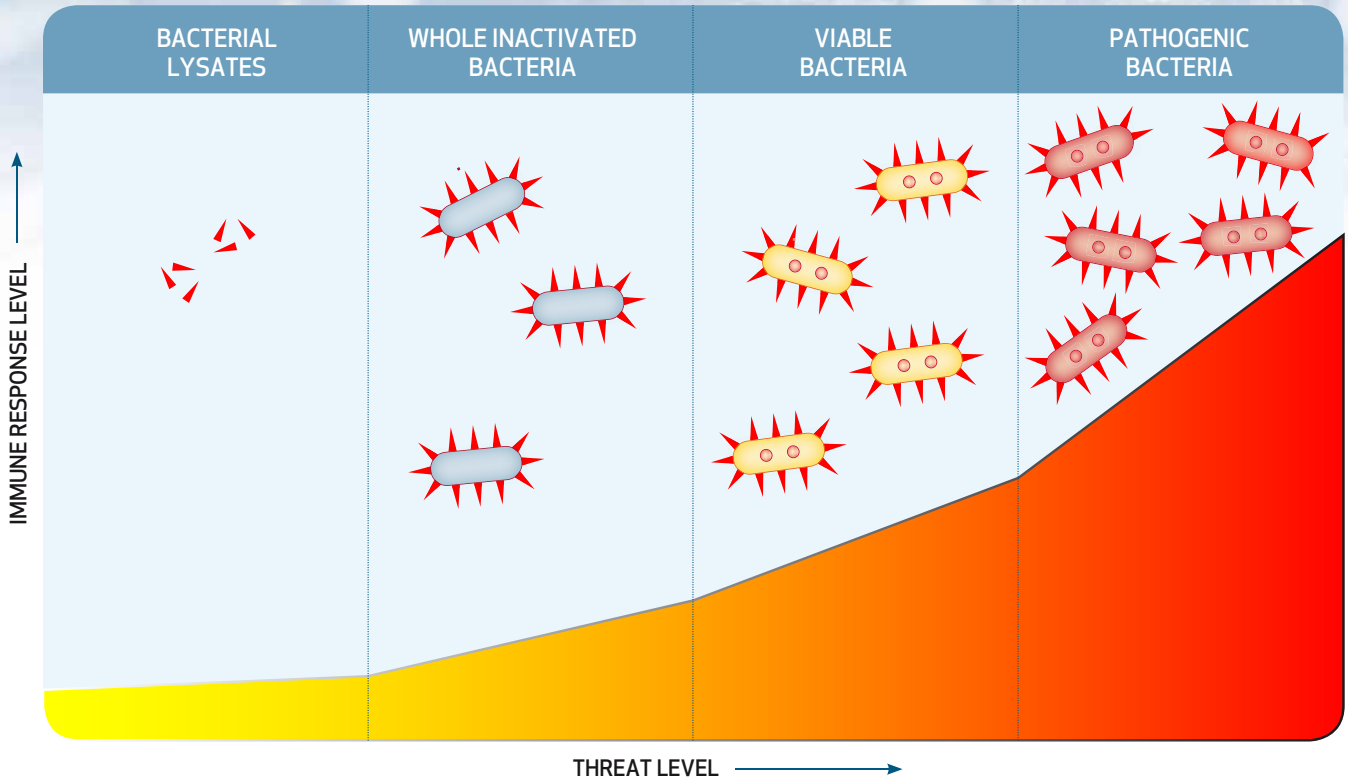
SPRAY

WHOLE BACTERIA *vs* BACTERIAL LYSATES

EFFECTIVENESS

UROMUNE® PERLINGUAL SPRAY

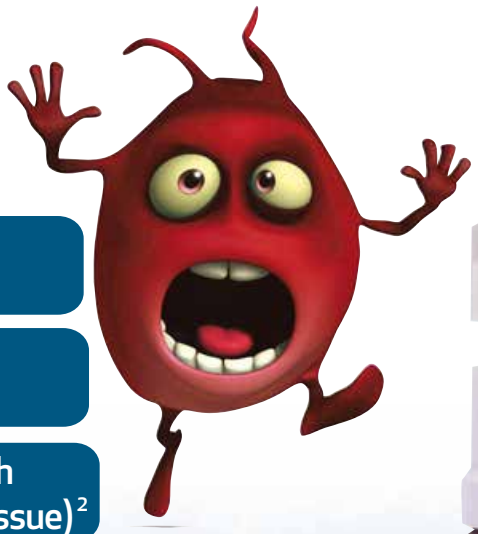
CORRELATION OF THE MICROBIAL THREAT WITH INFLAMMATORY RESPONSES



Adapted from: Blander *et al*. **"Beyond pattern recognition: five immune checkpoints for scaling the microbial threat"**. Nat Rev Immunol. 2012; Mar; 12(3):215-25.

SPRAY

HOW IT WORKS



01 **Dendritic cells** activation[1]

02 **Lymphoid tissue** response[2]

03 **Lymphoid recirculation** associated with MALT (Mucosa-Associated Lymphoid Tissue)[2]

04 **Immunomodulation** in the mucosa by intervention in **IgA production**[2]

05 **Reduction of urinary tract infections** [3]

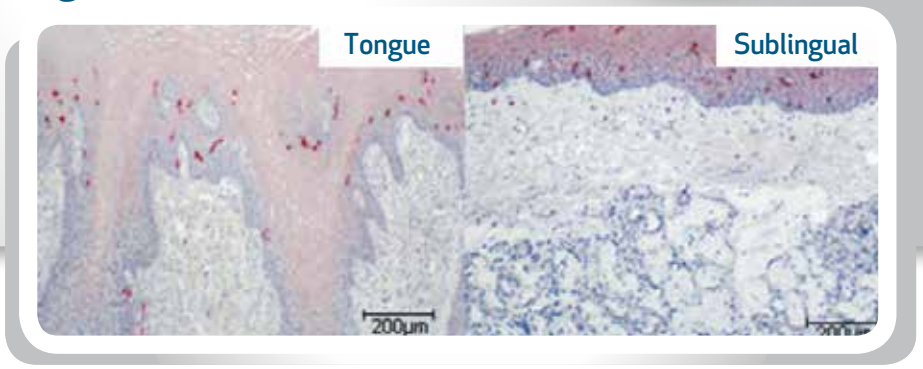
1 Benito-Villalvilla C, *et al*. **Immunological mechanisms activated by a polyvalent bacterial preparation used for the treatment of recurrent urinary tract infections (RUTIs)**. Allergy 2016; 71(S102):118–272.
2 Holmgren *et al*. **Mucosal immunity and vaccines**. Nature Medicine 11, S45 - S53 (2005).
3 Lorenzo-Gómez *et al*. **Evaluation of a therapeutic vaccine for the prevention of recurrent urinary tract infections versus prophylactic treatment with antibiotics**. Int Urogynecol J (2013) 24:127 – 134.

SPRAY **PERLINGUAL APPLICATION**

UROMUNE® PERLINGUAL SPRAY

- **Direct stimulation** of the **immune system** components present in the oral mucosa
- **Avoids** degradation caused by the **action of gastrointestinal secretions**
- **High bioavailability** by avoiding the degradation by the first hepatic transit and **speed** of action
- **Suitable** for patients with **swallowing disorders**
- **Pineapple flavor**

Allam JP, *et al*. **Distribution of Langerhans cells and mast cells within the human oral mucosa: new application sites of allergens in sublingual immunotherapy?**. Allergy 2008 Jun: 63(6): 720–727



SPRAY **STIMULATION OF THE MUCOSA**

	SUBLINGUAL	NASAL	ORAL
• Upper respiratory tract	+++	+++	-
• Lower respiratory tract	+++	+a+++	-
• Stomach	+/+++	-	+/+++
• Small intestine	+++	-	+++
• Colon	?	-	±
• Rectum	?	-	±
• Genital tract	+++	++	-
• Blood	++	+++	+

Adapted from: Çuruburu *et al*. **Vaccine. Sublingual immunization induces broad-based systemic and mucosal immune responses in mice**. Vaccine 25 (2007) 8598–8610
Czerkinsky *et al*. **Sublingual vaccination**. Human Vaccines (2011) 7:1, 110-114

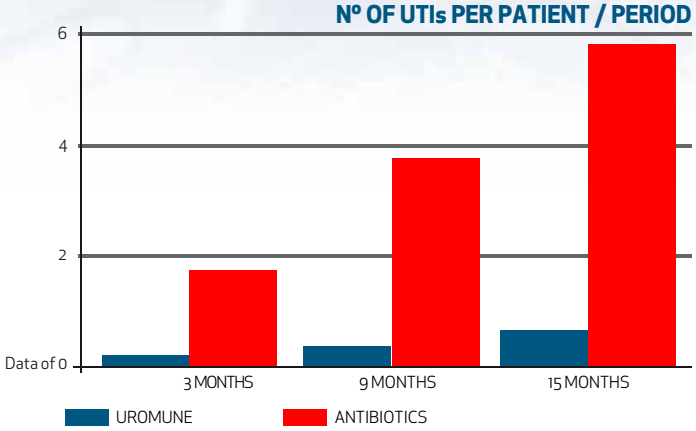
UROMUNE® PERLINGUAL SPRAY

SPRAY — REDUCES URINARY TRACT INFECTIONS

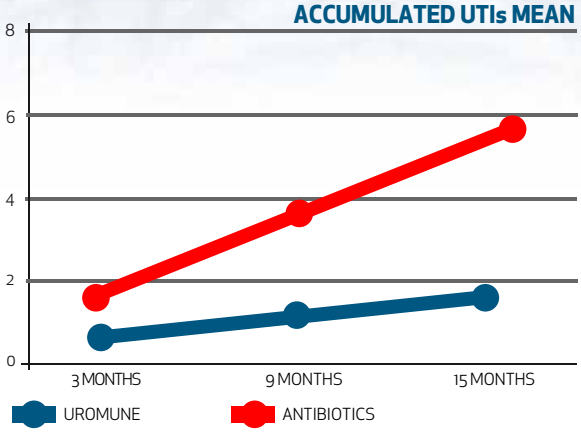
ITUs

- **Reduction** of UTIs (mean **78.2%**) in patients treated with Uromune® compared to those treated with antibiotics (sulfamethoxazol/trimethoprim) (P<0.0001)
- Uromune® **reduces 4** times the risk of suffering a UTI compared to conventional treatment.

Nº OF UTIs PER PATIENT / PERIOD



ACCUMULATED UTIs MEAN



MONTHS	UROMUNE®	ANTIBIOTIC	%
De 0 a 3 M	0,36	1,60	77,5
De 3 a 9 M	0,72	3,71	80,6
De 9 a 15 M	1,35	5.75	76,5

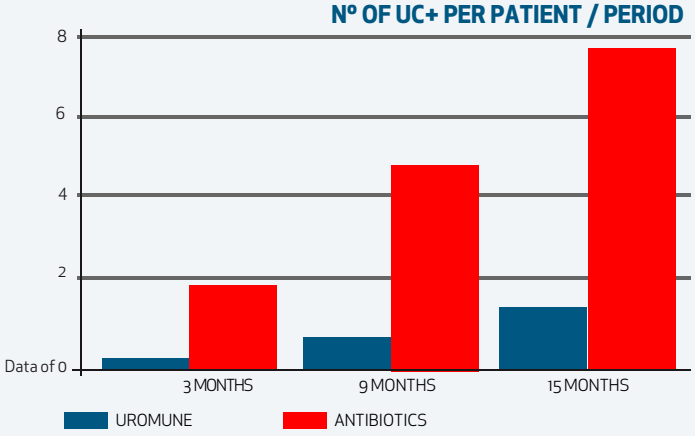
Lorenzo-Gómez *et al.* **Evaluation of a therapeutic vaccine for the prevention of recurrent urinary tract infections versus prophylactic treatment with antibiotics.**
Int. Urogynecol J (2013) 24:127 - 134

SPRAY — REDUCES POSITIVE UROCULTURES

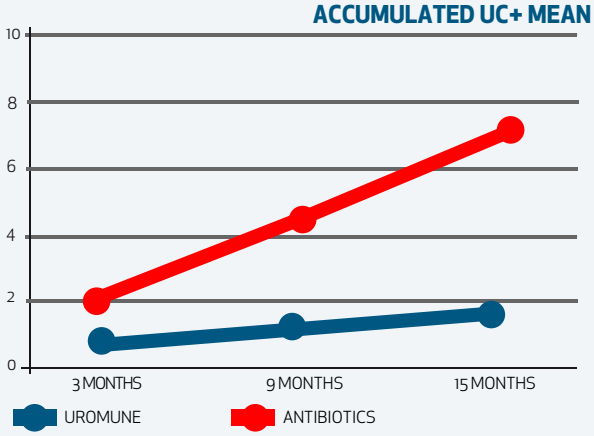
UC+

- **Reduction** of positive UC (mean **76.7%**) in patients treated with Uromune® compared to those treated with antibiotic. (P<0.0001)
- Uromune® **reduces by 7** times the positive urocultures with conventional treatment

Nº OF UC+ PER PATIENT / PERIOD



ACCUMULATED UC+ MEAN



MONTHS	UROMUNE®	ANTIBIOTIC	%
De 0 a 3 M	0,50	1,60	68,8
De 3 a 9 M	1,06	5,01	78,8
De 9 a 15 M	1,34	7,64	82,5

Lorenzo-Gómez *et al.* **Evaluation of a therapeutic vaccine for the prevention of recurrent urinary tract infections versus prophylactic treatment with antibiotics.**
Int. Urogynecol J (2013) 24:127 - 134

SPRAY

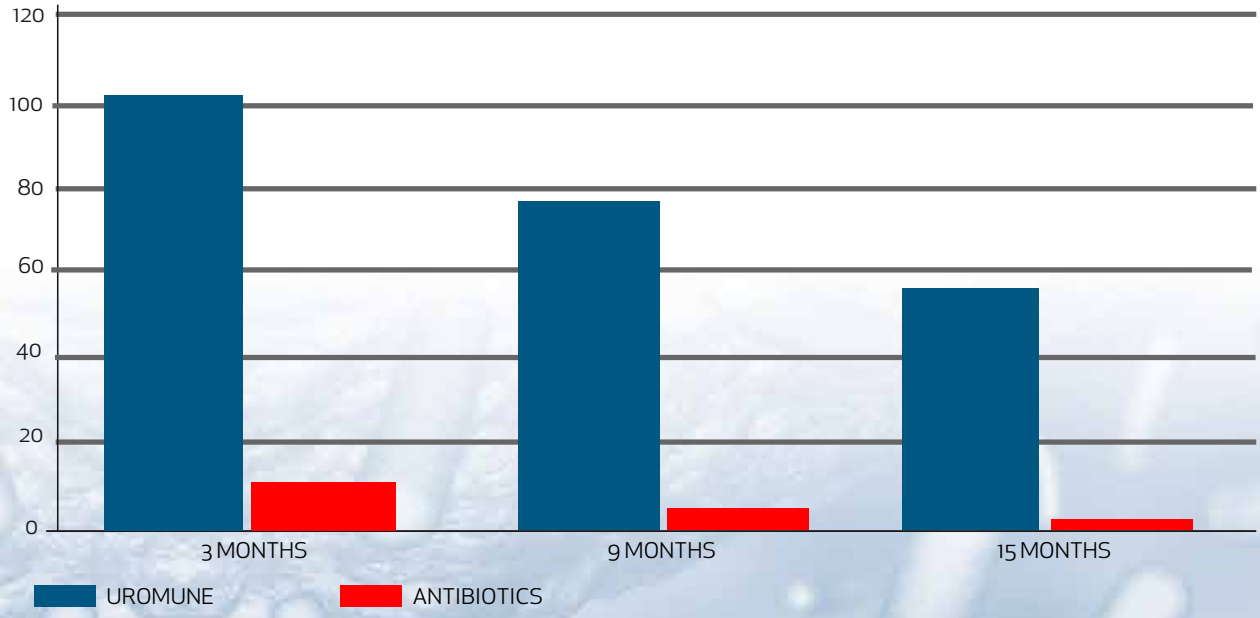
CLINICAL BENEFITS OF UROMUNE®

UROMUNE® PERLINGUAL SPRAY

STUDY CONDUCTED IN 319 PATENTS, FROM WHICH 159 WERE TREATED WITH UROMUNE® AND 160 WITH ANTIBIOTICS FOR 3 MONTHS

- **63.5%** of patients were free from UTIs in **3 months**
- **34.6%** of patients were free from UTIs in **15 months**

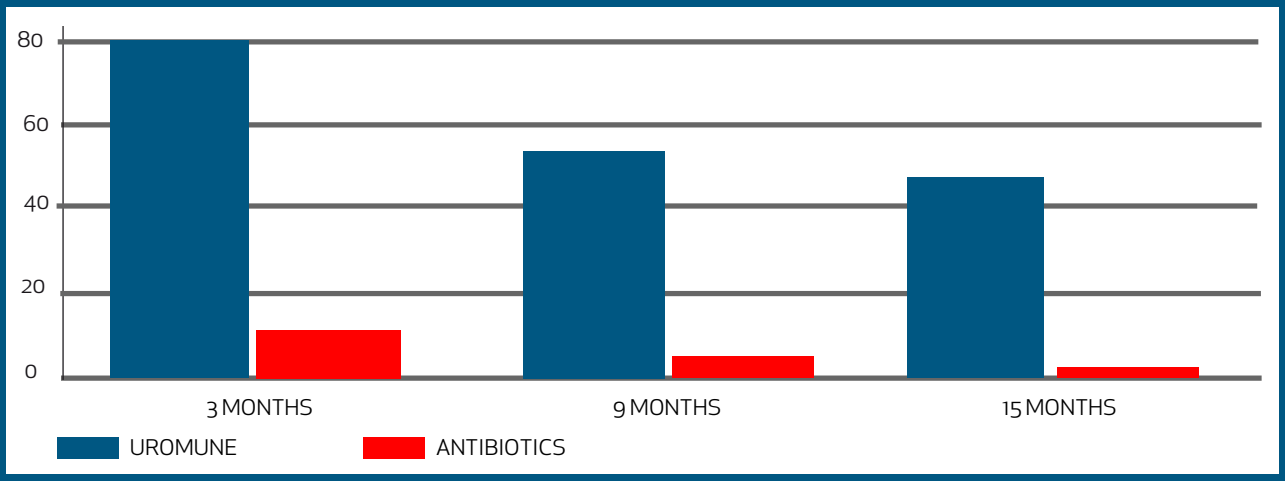
PATIENTS FREE FROM UTIs



Lorenzo-Gómez *et al*. **Evaluation of a therapeutic vaccine for the prevention of recurrent urinary tract infections versus prophylactic treatment with antibiotics.** Int. Urogynecol J (2013) 24:127 - 134

- **50.3%** of patients were free from UC+ in **3 months**
- **30.8%** of patients were free from UC+ in **15 months**

PATIENTS FREE FROM UC+

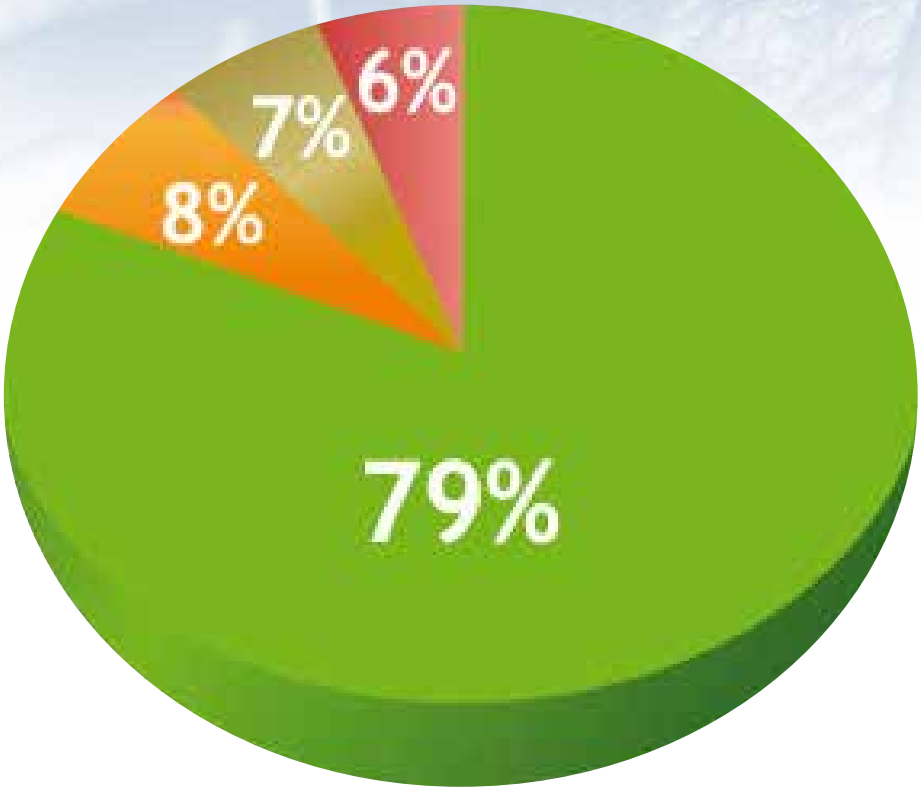


Lorenzo-Gómez *et al*. **Evaluation of a therapeutic vaccine for the prevention of recurrent urinary tract infections versus prophylactic treatment with antibiotics.** Int. Urogynecol J (2013) 24:127 - 134

SPRAY **RECOMMENDED FORMULATIONS OF UROMUNE**

UROMUNE® PERLINGUAL SPRAY

• Most common bacteria causing UTIs



UROMUNE® PERLINGUAL SPRAY

TREATMENT

2x

DAILY DOSE

2 vials of 9 mL. Treatment duration: 3 months approxymately
1 vial of 6 mL. Treatment duration: 1 month approxymately

UROMUNE® PERLINGUAL SPRAY

Urinary tract infections (UTIs)

BACTERIA	%
Escherichia coli	25
Klebsiella pneumoniae	25
Proteus vulgaris	25
Enterococcus faecalis	25

Antonia Andreu *et al*. **Etiology of community-acquired lower urinary infections and antimicrobial resistance of Escherichia coli: a national surveillance study**. Med Clin (Barc). 2008;130(13):481-6

Product Characteristics

UROMUNE® is a glycerinated suspension of four types of whole inactivated bacteria (300 FTU/mL (Formazin Turbidity Unit), 10^9 bacteria/mL) for sublingual specific immunotherapy (per-lingual).

Composition: glycerinated suspension containing four whole inactivated bacterial concentrates as active substances of the formulation: Klebsiella pneumoniae (25%), Escherichia coli (25%), Enterococcus faecalis (25%) and Proteus vulgaris (25%).

Excipients: Glycerol, artificial pineapple flavouring, sodium chloride and water for injection.

Pharmaceutical Form: The pharmaceutical product is a suspension for sublingual/per-lingual spraying of an adequate concentration of whole inactivated bacterial concentrates suspended in an isotonic saline solution with 50% glycerol, and packed in amber-glass bottles closed with a plastic cap, containing a spray pump and applicator for spraying, secured with a seal.

Presentations: Depending on the desired treatment duration, **UROMUNE®** is available in two presentations:
- **Monthly treatment:** 1 vial containing 6 ml.
- **Three-month treatment:** 2 vials containing 9 ml.

Therapeutic indications: UROMUNE® is an immunomodulator, for the prevention of recurrent urinary infections. Its function is to stimulate the immune system, thus enhancing its resistance against urinary tract infections. **UROMUNE®** can be administered to adults, children and breast-feeding mothers.

Administration instructions: UROMUNE® must be administered by spraying over the sublingual area (per-lingual route). **UROMUNE®** is to be self-administered by the patient at home. The adequate use of the spray container is as follows: Remove the plastic seal of the vial for the application. When opening each vial and before use, turn the pipette horizontally and spray 3 or 4 times to make sure that the dispenser is primed with enough solution to work properly. Turn aside the pipette and put it under the tongue, thus applying the product over the sublingual/per-lingual area. Spray the product. Do not swallow it immediately. Keep the solution under the tongue for 2 minutes and then swallow it. Once the administration is finished, turn the pipette into its original position in order to block the spray button, and place the bottle in its original package.

The posology consists of two daily applications. Patients should be warned not to eat or drink immediately before or after the intake of the vaccine in order to allow a maximum exposure and contact of the product with the area of administration.

Bibliographic References

Benito-Villalvilla C, *et al*. **Immunological mechanisms activated by a polyvalent bacterial preparation used for the treatment of recurrent urinary tract infections (RUTIs)**. Allergy 2016; 71(S102):118–272.

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