**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Uromune 300 FTU/mL, sublingual spray, suspension

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of suspension contains 300 FTU (approx. $10^9$ bacteria/mL) of MV140: inactivated bacterial strains of 25% *Escherichia coli* (V121), 25% *Klebsiella pneumoniae* (V113), *25% Enterococcus faecalis* (V125) and 25% *Proteus vulgaris* (V127). Concentration is defined as FTU/mL (Formazin Turbidity Units/mL).

Uromune is a glycerinated suspension containing four selected whole-cell, heat inactivated bacterial strains and their proportion in the formulation are as follows:
*Escherichia coli*…….. 25%
*Klebsiella pneumoniae*…….. 25%
*Enterococcus faecalis*…….. 25%
*Proteus vulgaris*…….. 25%

Excipient(s) with known effect
This medicine contains less than 1 mmol sodium (23 mg) per mL, that is to say essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Sublingual spray, suspension.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Uromune is a mucosal bacterial vaccine indicated in adults and pediatric patients (children and infants) for the prevention of recurrent urinary tract bacterial infections (rUTI).

### 4.2 Posology and method of administration

Posology
The recommended dose is 2 sprays per day in a single procedure (one dose is 2 sprays), for a final daily dose of 0.2 mL. The duration of the treatment would be approximately 90 days (3 months).

*Paediatric population*
Based on previous clinical experience, the recommended dose in children and infants is 2 sprays per day in a single procedure (one dose is 2 sprays), for a final daily dose of 0.2 mL.

Method of administration

Uromune is administered sublingually:

1. Remove the plastic seal from one bottle.

2. Gently shake the bottle.
3. Rotate the nozzle sideways. Spray 3 or 4 times to ensure the pump mechanism fills up (only when starting the bottle).

4. Lift your tongue and direct the nozzle under your tongue and spray twice to apply the appropriate dose.

5. Retain the dose under your tongue, for approximately 1-2 minutes before swallowing.

6. Rotate the nozzle back to its original vertical position, thereby locking the spray mechanism.

7. Return the bottle back to the box and store accordingly as referenced in section 5.

Uromune is packed in 2 bottles of 9 mL each. The duration of each bottle is approximately 45 days. Therefore, the course of the treatment would be approximately 90 days (3 months).

## 4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

## 4.4 Special warnings and precautions for use

Uromune with food and drink
Uromune must be administered as separate as possible from the intake of food and/or drinks (at least, 30 minutes prior and after the consumption of food and/or drinks). Do not brush your teeth or rinse the mouth within the 30 minutes prior or after administration.

Paediatric population
No special precautions are required for use in pediatric population.

## 4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

## 4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of Uromune in pregnant women.

Breast-feeding
There is insufficient information on the effects of Uromune in newborns/infants.

Fertility
No data are available.

Uromune contains completely inactivated microorganisms, thus without infectious capacity.

## 4.7 Effects on ability to drive and use machines

Uromune has no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

Gastrointestinal disorders sensation and/or discomfort in the oropharyngeal area, may rarely occur. The presence of the referred reactions does not imply that treatment should be interrupted or postponed, but supervision of the administration may be necessary.
The adverse reaction listed below were obtained from clinical trial data, spontaneus reports and from the medical literature.
Adverse drug reactions (ADR) are ranked by frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

| **System Organ Class** | **Very common (≥ 1/10)** | **Common (≥1/100 to <1/10)** | **Uncommon (≥ 1/1,000 to<1/100)** | **Rare (≥1/10,000 to<1/1,000)** | **Very rare (<1/10,000)** |
|---|---|---|---|---|---|
| Metabolism and nutrition disorders | | | | Decreased appetite | |
| Nervous system disorders | | | | Formication<br>Headache | |
| Eye disorders | | | | Eye pain | |
| Respiratory, thoracic and mediastinal | | | | Asthma/ Asthma aggravated<br>Upper-airway cough syndrome<br>Dyspnoea | |

| System Organ Class | Very common (≥ 1/10) | Common (≥1/100 to <1/10) | Uncommon (≥ 1/1,000 to<1/100) | Rare (≥1/10,000 to<1/1,000) | Very rare (<1/10,000) |
|---|---|---|---|---|---|
| Gastrointestinal disorders | | | Oral pain<br>Epigastric discomfort<br>Oral mucosal exfoliation<br>Dental discomfort<br>Dry mouth<br>Gastritis | Abdominal discomfort<br>Abdominal pain<br>Glossitis<br>Nausea<br>Diarrhoea<br>Gastrooesophageal reflux disease | |
| Skin and subcutaneous tissue disorders | | Pruritus | | Rash<br>Rash pruritic<br>Perioral dermatitis | |
| Musculoskeletal and connective tissue disorders | | | | Arthralgia<br>Pain in extremity | |
| General disorders and administration site conditions | | | Malaise | Feeling hot<br>Generalised oedema<br>Pain<br>Flushing | |

**Summary of the safety profile**

Most adverse reactions with Uromune are rare or very rare. These could be local (in the place of administration) or systemic.

Local reactions (oropharyngeal), although their frequency is low, are the events most commonly reported. Their presence does not imply that treatment should be interrupted or postponed, but supervision of the administration may be necessary.

Systemic side effects as malaise, rash, generalized pruritus may rarely appear. Also, there were reported very few cases of asthma or asthma aggravated, for this last referred event, treatment should be discontinued, and notification is strongly recommended.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

### 4.9 Overdose

No case of overdose with Uromune is known up to now. Due to the nature of Uromune, an overdosage seems unlikely to happen. In case of accidental overdosing or an incorrect administration, patients may experience some undesirable effects (see section 4.8 Undesirable effects).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other bacterial vaccines ATC code: J07AX

Mechanism of action
Uromune is a vaccine that works by stimulating the immune system, to increase the resistance against urinary tract infections.

Uromune is intended for secondary prevention in patients with rUTI.

The active substance of Uromune are those bacteria that are the main cause of UTIs. Uromune-contained bacteria are fully inactivated and cannot reach the bloodstream from the oral mucosa. Rather, they are actively taken up by oral dendritic cells (DCs). These cells will induce an adaptive local immune response (induction site), which spread to other mucosal tissues, such as the bladder (effector site).

Sublingual vaccination with Uromune induces a specific immune response (Th17/Th1), the main mechanism involved in resistance against bacterial bladder infections. It also induces a regulatory T-cell response, which together with the Th1 response, down-regulates detrimental Th2 responses associated with recurrence of bladder infection. These responses have been observed in vitro and in vivo in preclinical studies. In vivo studies have shown these responses in the spleen and distant (inguinal) lymph nodes following sublingual administration. Early TNFα responses are also observed in the bladder of sublingually immunized mice following simulation with bacteria contained in Uromune. In an experimental model of bladder infection with *Escherichia coli*, Uromune conferred an early protection that was associated with a rapid T cell response in the bladder along with an increased influx of myeloid cells in urine. Additionally, Uromune induces an antibody response including immunoglobulin A, G and M, against the bacteria contained in its formulation.

Pharmacodynamic effects
Its pharmacodynamic effect targets the immune system.

Clinical efficacy and safety
The efficacy and safety of Uromune on recurrent urinary tract bacterial infections was evaluated in a multicenter, randomized, double-blind, placebo controlled, parallel-group, one-year, phase III trial, including 240 women (18 to 75-year-old). Women that had suffered from at least 5 uncomplicated cystitis in the previous year were included and administered either placebo, or Uromune for 3 or 6 months. There was a follow-up of 12 months since the beginning of the treatment.

In the 9-month efficacy period (i.e. following 3 months of administration), the median of UTI episodes was 3.0 [interquartile range, IQR, 0.5-6.0] for placebo group compared to 0.0 [IQR, 0.0-1.0] in both groups receiving Uromune ($P$<0.001). Moreover, a significant increase in the UTI-free rate was found ($P$<0.001), being 25.0% in placebo group compared to 55.7% and 58.0% in subjects receiving Uromune

for 3 or 6 months, respectively. The median time until the appearance of the first UTI was significantly delayed in Uromune-receiving individuals, at least for 227 days. A very significant reduction was also found in symptom score, together with an important improvement in quality of life during the whole study period comparing active groups vs. placebo ($P$<0.001). The median of antibiotic score was 4.5 [IQR, 1.0-8.5] for placebo group, being reduced to 1.0 [IQR, 0.0-3.0] in both groups receiving Uromune ($P$<0.001) during the whole study period. Moreover, a significant decline in healthcare resource use was found, mostly associated to urologist visits and complementary tests. No differences between active treatment schedules were observed for any clinical variable.

Regarding safety, only 5 subjects (2.2%) reported non-serious adverse reactions, 2 from placebo and 3 from MV140 3-month group.

*Effectiveness and safety findings from Non-Interventional Studies*

In different observational studies, prophylaxis with Uromune demonstrated higher efficacy than prophylaxis with antibiotics in the management of rUTI, reducing the incidence of UTIs and increasing the infection-free period. Subjects treated with Uromune daily for three months (519 women in total) had significantly higher UTI-free rates (35–90%) than those on six months of antibiotic prophylaxis (0% in 499 women in total) over 15 months of follow-up ($P$<0.001 for all studies).

The bacterial preparation has also been successfully used in the UK. Women suffering rUTI, for whom conventional therapy had failed, were given Uromune for a period of 3 months. Most of participants (78%) remained infection-free after the follow-up period (12 months), suggesting that Uromune is effective at preventing UTI recurrence in women. Another prospective study including almost 800 subjects showed that Uromune significantly reduced UTI episodes both in men and women. Finally, the last study, including women with different risk factors associated to UTI, demonstrated that Uromune conferred a protection that persisted, at least partially, for 2 years since initiation of the treatment. Herein, Uromune strongly reduced antibiotic consumption and healthcare-associated costs of UTI.

Other studies evaluating subjects with complicated UTI consistently reported favorable UTI-free rates ranging from 30-50%, significant UTI reduction rates and improved quality of life. One of these studies included patients with autoimmune diseases, where immunosuppressive treatments make them prone to suffer infectious episodes. Both the number of UTI episodes, antibiotic consumption, and the need of healthcare resources, assessed 12 months after initiating a 3-month treatment course with Uromune, were significantly reduced compared to the year prior to vaccination.

Some previous studies including women aged 16-18 years and different case reports in children aged 6 to 12, coming up from real life clinical experience, have demonstrated the clinical benefit conferred by Uromune in the paediatric population. Most of the children reported no recurrences or reduced the incidence of UTIs, decreasing the severity of infectious episodes (asymptomatic bacteriuria or no febrile UTIs)

The above-mentioned studies have been systematically reviewed, concluding that Uromune provides a 2- to 6-fold reduction of UTIs in a 12-month period, with up to 90% of patients remaining totally free of infection. These outstanding results have been highlighted, placing Uromune as a highly promising non-antibiotic alternative for prevention and management of rUTI.

The frail elderly study shows that, following bacterial immunoprophylaxis, the number of UTIs significantly decreased 12 months following treatment with either autovaccine or MV140, compared to the episodes before vaccination in all treatment groups, both males and females. The median number of UTIs after prophylaxis ranged from 0.0 to 0.3 episodes per month, depending on the study group.

Overall, the rate of reduction ranged from 7-fold for subjects receiving a new course of autovaccine to 40-fold for women on first treatment with MV140. Noteworthy, in all groups, a significantly greater reduction in UTIs was observed in individuals who received MV140 compared to those who received autovaccines. Regarding the proportion of UTI-free subjects, up to 60% of individuals receiving MV140 remained totally free of urinary infections at the end of the follow-up period, but none from autovaccine groups. No differences in UTI number between sex, nor first treatment and boost-receiving groups were found at the end of the study.

Several studies using Uromune as a preventing treatment in patients with rUTI report a good tolerance and lack of adverse reactions during and after 3 months of Uromune daily intake. In the post-marketing surveys, with thousands of Uromune treatments administered, a total of 13 cases of adverse reactions were reported spontaneously in the last 6 years' experience worldwide using Uromune.

### 5.2 Pharmacokinetic properties

Due to the administration route, the active substances (inactivated bacterial strains) are not absorbed into the vascular system. Thus, no pharmacokinetic studies in either animals or clinical studies investigating the pharmacokinetic profile and metabolism of Uromune have been conducted.

### 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, local tolerance, as well as safety evaluated during pharmacodynamic/mechanistic studies.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Glycerol (E-422)
Sodium chloride
Artificial pinapple flavouring (containing propylene glycol)
Water for injection

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

### 6.5 Nature and contents of container

Uromune is packed in 2 bottles of 9 mL each.

The container closure system consists in:

- Primary packaging: Type III amber glass bottles, closed with a white plastic applicator with an integrated pump spray inserted.
- Secondary packaging: white resistant plastic box filled in with a foam material that will contain and protect the bottles.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

INMUNOTEK, S.L.
Calle Punto Mobi 5, Alcalá de Henares, 28805. Madrid, SPAIN.
Phone: +34 912 908 942
Fax: +34 902 906 841
vac@inmunotek.com

## 8. MARKETING AUTHORISATION NUMBER(S)

N/A

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

N/A

## 10. DATE OF REVISION OF THE TEXT

04/2022