SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Uralyt-U

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:

Each measuring spoonful of 2.5 g granules contains:
Potassium sodium hydrogen citrate (6:6:3:5) 2.427 g

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Granules,

Pale orange- colored fine grained granules with aromatic odour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

To dissolve uric acid stones in the urinary tract.
Prevention of further stone formation.
Note: This product administration should be used as part of a general concept of metaphylaxis (i.e. diet, increased fluid uptake etc.).

Mechanism of Action
Uric acid is sparingly soluble or completely insoluble in solutions of greater acidity (i.e. pH below 6), and under these conditions, it forms crystals and in unfavourable circumstances may grow into stones. Uralyt-U action is based on the fact that it can stabilize the pH of urine within the correct pH range of 6.2 to 6.8. Thus Uralyt-U improves the solubility of uric acid and prevents the formation of uric acid crystals (stones) and also re-dissolves any crystals (stones) that are already present. Uralyt-U is free from carbohydrates and can therefore safely be taken by diabetics.

4.2 Posology and method of administration

Posology

a) Dissolution and metaphylaxis of uric acid stones:

In general, take 4 measuring spoonfuls (= 10 g of granules equivalent to 88 mmol of alkali) daily divided into three doses, after meals.

Take 1 measuring spoonful every morning, 1 measuring spoonful at midday and 2 measuring spoonfuls every evening.

The pH value of the freshly voided urine should be within the range of pH 6.2 – 6.8.

If the pH value is below the specified range, the daily dose should be increased by half a measuring spoonful of **Uralyt-U** (11 mmol of alkali) in the evening. If the pH is above the specified range, the daily dose should be reduced by half a measuring spoonful (11 mmol of alkali) in the evening.

The correct dosage has been reached if the pH value of the freshly voided urine,

measured before taking the dose of **Uralyt-U**, is within the specified range.

For metaphylaxis of uric acid stones, regular checks of the urine pH levels are recommended.

b) Metaphylaxis of calcium-containing renal calculi:

The daily dose should be 2 - 3 measuring spoonfuls (= 5 - 7.5 g of granules equivalent to 44 mmol - 66 mmol of alkali) and should be taken in a single dose in the evening. If the measured pH value is too low, 3 - 4.5 measuring spoonfuls (= 7.5 g - 11.25 g of granules equivalent to 66 - 99 mmol of alkali) should be taken in 2-3 doses divided over the day, after meals.

The target PH value should be 7.. The pH value should not be lower than 6.2 and should not exceed pH 7.4.

Citrate levels and/or urine pH values should be regularly checked, and the individual dose (see above) adjusted accordingly.

Paediatric population

No data are available.

Method of administration:

The granules should be taken as a solution in a glass of water.

Measurement of urine pH value:

Immediately before taking each dose, a test strip of the indicator paper enclosed in this pack should be wetted with freshly voided urine.

The colour of the wet test strip shall then be compared with the colour chart, and the pH value printed below the corresponding colour can be read off.

This pH reading as well as the number of measuring spoonfuls of granules taken should be noted in the control calendar. The patient ought to bring the control calendar every time he visits the doctor.

4.3 Contraindications

In the patient information leaflet, it is pointed out to the patient that

Uralyt-U® should not be usedin cases of :

- Impaired renal excretory function -
- Metabolic alkalosis
- Hyperkalemia
- Adynamia episodica hereditaria
- Chronic urinary tract infections with urea-splitting bacteria (danger of formation of struvit stones)
- Low sodium diet
- in case of increased sensitivity against ingredients of **Uralyt-U®**:
- Hypersensitivity to the active substance, or to any of the excipients listed in section 6.1.

Note:
The treatment of children less than 12 years of age is not recommended as there is not enough clinical experience for this age group.

4.4 Special warnings and special precautions for use

Before starting treatment all circumstances/malconditions that may cause urinary stones and for which well-targeted therapy is available (such as adenoma of parathyroid glands, malignancy associated with uric acid stones etc.) should be ruled out.

The maximum recommended daily dose is 11.25 g of granules (4.5 measuring spoonful's). This is equivalent to 1.86 g of potassium and 1.09 g of sodium, i. e. 47.5 mmol potassium of and 47.5 mmol of sodium. This should be considered in particular when treating the elderly and in case of concomitant therapy with potassium-saving diuretics, aldosterone antagonists, ACE-inhibitors,

angiotensin receptor antagonists, non-steroidal anti-inflammatory drugs or peripheral analgesics. Interaction with these medicinal products can lead to hyperkalaemia.

Before taking the first dose the serum electrolytes should be determined and renal function should be monitored. Furthermore, the acid- base status should be checked when renal tubular acidosis (RTA) is suspected.

Uralyt-U should be used with caution in patients with severely impaired liver function.

This medicinal product contains the colouring agent Yellow orange S (E110) which may induce allergic reactions including asthma in sensitized persons. Allergy is more often seen in people reacting to 2-acetoxybenzoic acid (acetylsalicylic acid).

4.5 Interaction with other medicinal products and other forms of interactions

Any increase in extracellular potassium concentration will weaken the effect of cardiac glycosides, while any decrease will potentiate the arrhythmogenic effect of cardiac glycosides.

If taken concomitantly with other potassium containing medicinal products, hyperkalaemia may occur.

Aldosterone antagonists, potassium-saving diuretics, ACE inhibitors, angiotensin receptor antagonists, non-steroidal anti-inflammatory drugs and peripheral analgesics reduce renal potassium excretion. Attention should be paid to the fact that 1.0 g of potassium-sodium-hydrogen citrate contains 0.172 g or 4.4 mmol of potassium.

When prescribing a low sodium diet, please remember that 1.0 potassium-sodium-hydrogencitrate contains 0.1 g or 4.4 mmol sodium, equivalent to 0.26 g sodium chloride.

Concomitant administration of substances containing citrate aluminium can lead to increased aluminium absorption; if such medicines need to be taken, an interval of at least 2 hours must be allowed between taking each kind of product.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of **Uralyt-U** in pregnant women. Animal studies do not indicate direct or harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, the use of **Uralyt-U®** during pregnancy should be avoided. If administration during pregnancy is necessary, maternal plasma levels of sodium and potassium should be monitored regularly.

As long as maternal plasma levels remain in the physiological range, no harmful effects on the unborn child are to be expected.

Breastfeeding

There are no data from the use of Uralyt-U in breastfeeding women. As long as the mother's plasma levels of sodium and potassium remain in the physiological range after use of Uralyt-U, no harmful effects are expected on the breastfed child and Uralyt-U can be used during lactation.

Fertility

There are no clinical data on the effects of Uralyt-U on male and female fertility. It is unlikely that the active ingredients directly affect fertility in either females or males as sodium potassium and citrate participate in normal physiological processes in the body and are part of the normal diet.

4.7 Effects on ability to drive and use machines

Uralyt-U has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

The rating for side effects is based on the following frequency convention:

Very common	≥ 1/10
Common	≥ 1/100 - < 1/10
Uncommon	≥ 1/1.000 - < 1/100
Rare	≥ 1/10.000 - < 1/1.000
Very rare	< 1/10.000
Not known	Frequency cannot be estimated from the available data

Gastrointestinal disorders:

Mild gastric or abdominal pain are common. In rare cases, mild diarrhoea and nausea may occur.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the product is important.

It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form **https://sideeffects.health.gov.il**

4.9 Overdose

Overdose can lead to hyperkalaemia (potassium-plasma level >5 mmol/l), in particular in patients with simultaneous acidosis or renal failure.

Provided that renal function is adequate, there is no likelihood of any unwanted effects on normal metabolic physiological parameters, even after taking doses higher than those recommended, since the excretion of any base excess via the kidney provides a natural regulatory mechanism which ensures maintenance of the acid-base balance.

Any rise above the recommended urine pH-range should in no circumstances be allowed to persist for more than a few days, since at considerably high pH levels there is an increased risk of phosphate crystallisation. On the other hand, the long-term establishment of a definite alkalotic metabolic state is undesirable. Inadvertent overdosage can be corrected at any time by reducing the dose: if necessary appropriate measures for the treatment of metabolic alkalosis may be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alkali citrates, agents for urolithiasis

ATC: **G04BC01**

Salts of strong bases with weak acids are suitable for alkalinization (neutralisation therapy), and the acid component is assumed to be metabolizable. The citrate ion from alkali citrates undergoes almost complete oxidative metabolic breakdown to CO_2 or bicarbonate. The base excess resulting from the remaining alkali ions is eliminated via the kidneys and produces an increase in urine pH value.

Neutralisation or alkalinization of the urine can be achieved by oral administration of alkali citrates, the response being dose-dependent.

1 g of potassium sodium hydrogen citrate (8.8 mmol of alkali) causes the urine pH value to increase by 0.2 – 0.3 units. As a result, the dissociation rate increases and thus the solubility of uric acid. Litholysis of uric acid calculi is radiologically demonstrated.

Serum concentration of bicarbonate (negatively charged base excess) isthe regulator of citrate excretion. Negatively charged base excess induces alkalosis via a shift in intracellular pHvalue.

This leads to alkaloisis-induced inhibition of renal tubular metabolism of citrate what results in reduced reabsorption of citrate and increased citrate excretion.

At the same time, alkaloids has an influence on renal calcium flux by significantly reducing urinary calcium excretion.

Alkalisation of urine, increased excretion of citrate and reduced excretion in calcium, lead to a decrease of the activity product of calcium oxalate, as citrate in weak alkalotic milieu forms stable complexes with calcium

Moreover, the citrate ion must be regarded as the most effective physiological inhibitor of calcium oxalate (and calcium phosphate) crystallisation and aggregation of these crystals.

To assess the usefulness of urinary alkalisation in following kinds of illness, data from systematic trials. are lacking. Observations in single cases as well as theoretical considerations speak for a therapeutic effect:

- Cystinuria and cystine stone formation: Alkalisation of urine increases the solubility of cystine. However, pH should arrive at values ranging between 7.5 and 8.5.

- Treatment with cytostatics: Alkalisation of urine in order to eliminate the rise in uric acid makes sense during a treatment with cytostatics. This is in line with the prophylaxis of uric acid stones, claimed as therapeutic indication. In addition, a protective effect of alkalotic urinary pH value is claimed because of reduced aggressivity of cytostatic metabolites (e.g. oxazaphosphorin cytostatics) and their increased solubility (e.g. methotrexate) respectively. For this purpose, urinary pH level should be regulated to a value of 7.0 at least.

- Porphyria cutanea tarda: In porphyria cutanea tarda, an uroporphyrinogen decarboxylase deficiency exists which metabolises uroporphyrinogen to coproporphyrinogen. The objective of metabolic alkalisation is to prevent back diffusion of coproporphyrin through renal tubuli so that the coproporphyrin clearance will increase. As a consequence of the increased coproporphyrinogen excretion, the synthesis of coproporphyrinogen from uroporphyrinogen is believed to increase and is consequently accompanied by a decrease in circulating uroporphyrin. Urinary pH levels should be adjusted to range between of 7.2 - 7.5.

5.2 Pharmacokinetic properties

Citrate undergoes almost complete metabolic breakdown. Only 1.5 % to 2% of the original administrated dose appears unchanged in the urine.

Intake of 10 g of potassium sodium hydrogen citrate yields approximately 36 mmol of citrate; this is equivalent to less than 2 % of the daily turnover of citrate involved in energy metabolism within the body.

After a one-day intake of potassium sodium hydrogen citrate the equivalent amounts of sodium and potassium are quantitatively excreted via the kidneys within 24 - 48 hours. During long-term administration, daily excretion of sodium and potassium is in equilibrium with the daily intake.

No significant changes in blood gases or in serum electrolytes have been observed. This indicates that by virtue of renal regulation of alkalinization, the acid-base balance of the body remains intact and that, provided renal function is adequate, any possibility of accumulation of sodium or potassium can be excluded.

5.3 Preclinical safety data

According to the results obtained from investigations in animals, potassium sodium hydrogen citrate (6:6:3:5) has toxicological potential in the prescribed dosage. Chronic tests in rats revealed that oral doses between 1 g / kg and less than 3 g / kgof bodyweight were safe.

Toxicological tests on reproduction in rats and rabbits at 2 g / kg of bodyweight revealed no teratogenic or embryotoxic/fetotoxic effects.

When observing the contraindications and notes, no cancerogenic and mutagenic effects are to be expected for the intended mode and duration of use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water,

Aroma: Lemon oil,

Colouring agent : Yellow orange S (E 110).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C.

After first opening, use within 6 months.

6.5 Nature and contents of container

Original packs with 280 g of granules.

The packs also contain: measuring polystyrene spoon, pH indicator paper and control calendars.

6.6 Special precautions for disposal and other handling of the product

No special requirements.

7. MANUFACTURER

Madaus GmbH
51101 Cologne, Germany

8. LICENSE HOLDER

Megapharm Ltd., 15 Ha'tidhar street, Ra'anana,Israel

9. ISRAEL LICENSE NUMBER

063-87-22365

10. Revised in November 2024 according to MOHs guidelines.

URA_SPC_112024_P.1