SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Uralyt-U

Granules for the preparation of an oral solution

Active ingredient: potassium sodium hydrogen citrate (6:6:3:5)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:

1 measuring spoonful of granules (2.5 g) contains:
potassium sodium hydrogen citrate (6:6:3:5) 2.4 g

For the complete listing of other ingredients see section 6.1.

3. PHARMACEUTICAL FORM

Granules

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

To dissolve uric acid stones in the urinary tract.
Prevention of further stone formation.

Note: Product administration should be 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

a) Dissolution and metaphylaxis of uric acid stones:

In general, take 4 measuring spoonfuls (= 10 g granules equivalent to 88 mmol 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 of the fresh urine should be within the range of pH 6.2 – 6.8.

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

The correct dose has been reached if the pH of the fresh urine, before taking the dose of **Uralyt-U**, is within the recommended range.

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

b) Metaphylaxis of calcium-containing renal calculi:

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

A urine pH reading of 7.0 should be aimed at. The pH should not fall below pH 6.2 and should not rise above pH 7.4.

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

Method of administration:

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

Measurement of urine pH:

Immediately before taking each dose, a test strip of the indicator paper enclosed in this pack should be wetted with fresh urine using the clamp enclosed also in this pack.

The colour of the wet strip is then compared with the colour chart and the pH printed below the corresponding colour is read off.

This pH reading and the number of measuring spoonfuls of granules taken should be entered 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 used

- in cases of acute or chronic renal failure
- in metabolic alkalosis
- Hyperkalemia
- with Adynamia episodica hereditaria
- in chronic urinary tract infections with urea-splitting bacteria (danger of generation of struvit stones)
- in low sodium diet
- in case of increased sensitivity against ingredients of **Uralyt-U**

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 therapy all circumstances/malconditions that may be in favour of urinary stones should be excluded. The same is true if there exists a specific therapy (adenoma of parathyroid glands, malignoma with generation of uric acid stones etc.).

The recommended daily dose is 11.25 g granulate (4.5 measuring spoons). This corresponds to 1.86 g potassium and 1.09 g sodium, i. e. 47.5 mmol potassium and 47.5 mmol sodium. This should be considered in the elderly and at simultaneous 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 hyperkalemia.

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.

Be cautious with the use of **Uralyt-U** in patients with severe disturbances of liver function.

This drug contains the colouring agent yellow orange S (E110) which may induce allergic reactions including asthma in a sensitized person. 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 interaction

Any increase in extracellular potassium concentration will weaken the effect of cardiac glycosides, while any decrease will potentiate the arrhythmogenic effect of cardiac glycosides. Aldosterone antagonists, potassium-saving diuretics, ACE inhibitors, angiotensin receptor antagonists, nonsteroidal anti-inflammatory drugs and peripheral analgesics diminish renal potassium excretion. Remember that 1.0 g potassium-sodium-hydrogencitrate contains 0.172 g or 4.4 mmol 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.

Drugs containing citrate given at the same time as drugs containing aluminium can cause an increase in aluminium absorption; if such drugs have to be taken, an interval of at least 2 hours must be allowed between taking each kind of drug.

4.6 Pregnancy and lactation

There are not enough clinical data about the use of **Uralyt-U** in pregnant women. Experimental studies in animals did not reveal any hints of teratogenic or embryotoxic effects. As the active ingredient is a combination of physiologically occurring substances, **Uralyt-U** may be used in pregnancy and lactation under the indicated dose recommendations.

Hints for harmful effects during pregnancy and lactation are not known

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Side effects' rating was based on the following frequency data:

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

Gastrointestinal disorders:

Mild gastric or abdominal pain are common. Mild diarrhoea and nausea are rare.

Other possible adverse reactions:

Yellow orange S (E110) which may provoke allergic reactions

4.9 Overdose

Overdose can lead to Hyperkalemia (potassium-plasma level >5 mmol/l), especially 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 parameters, even after taking doses higher than those recommended, since the excretion of any base excess by the kidney provides a natural regulatory mechanism which ensures maintenance of 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 and the long-term establishment of a definite alkalotic metabolic state is in any case 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, substances dissolving urinary concrements,

ATC: **G04BC01**

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

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 alkali) causes the urine pH to increase by 0.2 – 0.3 units. As a result dissociation rate increases and hence the solubility of uric acid. Litholysis of uric acid calculi is radiologically demonstrated.

Serum concentration of bicarbonate (negatively charged base excess) is, among others, the regulator of citrate excretion. Negatively charged base excess induces alkalosis via change of intracellular pH. Alkalosis inhibits tubular metabolism of citrate in the kidney that results in reduced absorption of citrate and increased citrate excretion.

Alkalosis at the same time has an influence on calcium flux and reduces urinary calcium excretion.

These mechanisms, namely alkalisation of urine, increased excretion of citrate and reduced excretion of calcium, lead to a decrease of the activity product of calcium oxalate, as citrate in weak alkalotic milieu forms stable complexes with calcium (antagonism of supersaturation of lithogenic constituents).

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

Evidence of usefulness of alkalisation is hampered in ensuing kinds of illness, which lack in systematic trials. Theoretical considerations as well as observations in single cases speak for a therapeutic effect:

- Cystinuria and cystine calculus formation: Alkalisation of urine increases solubility of cystine. Urinary pH should arrive at values 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. In addition, a protective effect of alkalotic urinary pH is claimed because of reduced agressivity of cytostatic metabolites (e.g. oxazaphosphorin cytostatics) and the increased solubility of cytostatic and its metabolites (e.g. methotrexate) respectively. Urinary pH should be regulated to a value of 7.0 at least.

- 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 rises. As a result 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 should meet a value of 7.2 - 7.5.

5.2 Pharmacokinetic properties

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

Ingestion of 10 g 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, the 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 very low toxicity in the prescribed dosage. Chronic tests in rats revealed that oral doses up to 1 g / kg, or less than 3 g / kg, bodyweight were safe.

Toxicological tests on reproduction in rats and rabbits at 2 g / kg 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 of use and duration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lemon oil (aroma), yellow orange S (E 110) (colouring agent).

6.2 Incompatibilities

Not known.

6.3 Shelf life

5 years.

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

The packs also contain indicator paper and control calendars.

6.6 Instructions for use and handling and disposal

No special requirements.

7. MANUFACTURER

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51101 Cologne, Germany

8. LICENSE HOLDER

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9. ISRAEL LICENSE NUMBER

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