

URALYT-U Madaus GmbH

For dissolving uric acid stones

Presentation

Manufacturer's packs of 280 g granules

To enable patients to manage their own treatment the following items are included in each pack of Uralyt-U:

- Directions for use
- Measurespoon (for 2.5 g of granules)
- Chart for recording dosage and pH readings
- Uralyt-U indicator paper (pH 5.2 - 7.4) for measuring urine pH.

Composition

1 measure spoonful of 2.5g of granules contains:

Potassium sodium hydrogen citrate (6:6:3:5) 2.4 g

Mode of action

Any increase in the amount of uric acid excreted in the urine may lead to the formation or uric acid stones. Such stones arise only in acid urine, and the solubility of uric acid can be increased by shifting urine pH towards the alkaline side. In this way any existing calculi can be dissolved and the formation of fresh stones can be prevented. Urine pH can be adjusted to the exact level required by regulating the dose of Uralyt-U.

Uses

- For dissolving uric acid stones and preventing the formation of fresh stones
- As a supportive measure in the treatment of cystine stones and cystinuria
- To alkalinize the urine during uricosuric treatment of cytostatic therapy
- For symptomatic therapy in porphyria cutanea tarda.

Dosage

In ordinary circumstances a daily amount of 4 measurespoonfuls (=10g of granules) should be taken in three separate portions after meals: 1 measure-spoonful in the early morning, 1 at midday and 2 in the evening.

The granules should be dissolved in a glass of water and drunk.

The pH reading of the fresh urine should be kept within the following pH ranges:

Uric acid stones and uricosuric therapy:	pH 6.2 - 6.8
Cystine stones:	pH 7.5 - 8.5
Cytostatic therapy:	at least pH 7
Porphyria cutanea tarda:	pH 7.2 - 7.5

If the pH is below the stated range the evening dose should be raised by half a measurespoonful. If the pH is above the stated range the evening dose should be lowered by half a measurespoonful.

When the pH of fresh urine tested before taking Uralyt-U is consistently within the stated range, patient and physician can be confident that the correct dose has been found.

Measurement of urine pH.

Immediately before taking each dose, one test strip from the block of indicator paper included in the pack should be moistened with fresh urine. For this purpose it should be held in the clip supplied. The moist test strip is then matched with the colour table and the corresponding pH is read off.

The pH reading and the number of measurespoonfuls of granules taken each day must be entered on the chart. The patient should bring the chart every time he visits the doctor.

The indicator paper supplied with the pack is not suitable for checking urine pH during treatment of cystine stones or porphyria cutanea tarda. For this purpose the physician can prescribe special indicator paper covering the range pH 7.2 - 9.7. The chart supplied with the pack can be used provided that the pH readings (colour numbers) at the head of the column are appropriately altered.

Dosage and administration

As a general rule, initial dosage should be regulated under medical supervision to meet individual needs.

In principle, the dose of Uralyt-U should be governed by its effect. This means that urine pH should be measured before each dose, so that the correct dose can be chosen. The measure spoon supplied with the pack enables the necessary dose to be measured with sufficient accuracy.

The average or normal daily dose is 4 measure-spoonfuls, filled and levelled, this being equivalent to 10 g of the granulate. It should be spread as uniformly as possible over the day.

	Every morning (around 0700-0800 hrs)	At midday (around 1400-1500 hrs)	Every evening (if possible around 2200 hrs)
Number of measure-spoonfuls (level)	1	1	2

The granules should be dissolved in liquid (water or fruit juice) and drunk after meals.

The effect should be checked immediately before taking the next dose of Uralyt-U by measuring the pH of the urine with the aid of the Uralyt-U indicator paper supplied (pH range 5.2 - 7.4).

This provides a guide to the dose required to shift urine pH into the optimal solubility range of 6.2 - 6.8. In no circumstances should the pH allowed to remain below or above this range.

The patient should immediately compare the test strip with the colour scale, read off the pH and enter the result on the chart. (The physician must be on the alert for visual defects, in particular colour blindness!).

If the pH is outside the correct range it must be adjusted at once by raising or lowering the next dose of Uralyt-U. As a guide to the amount required, 1 g of Uralyt-U (approximately half a measure-spoonful) will raise urine pH in an adult by approximately 0.2 - 0.3 units).

In addition to its primary influence on the pH-dependent solubility of uric acid, Uralyt-U has additional effects on the excretion of lithogenic and inhibitor substances (calcium, citrate ions) and thus tends to enhance the solubility of calcium oxalate. Furthermore, within the recommended pH range

solubility conditions for calcium phosphates remain favourable, and neither calcium hydrogen phosphate nor tertiary calcium phosphate can crystallize out.

Uralyt-U acts quickly and the shift in urine pH ensues immediately after taking the first dose. The patient can therefore adjust urine pH to the optimal range within a few days and can ascertain his or her individual dosage limits.

Duration of administration

How long should treatment continue? The answer differs from case to case. The time required for complete dissolution of pure uric acid stones averages from 5 - 12 weeks. Neutralization of the urine with Uralyt-U should be continued for at least 3 months after the stones have been completely dissolved so as to prevent early recurrence.

Long-term prevention

To prevent stone formation it is essential to check urine pH with the special indicator paper even after treatment with Uralyt-U has been discontinued. Should the urine pH drop again into the acid range resumption of treatment with Uralyt-U is advisable as a safeguard against the risk of renewed stone formation.

Good results in the long-term prevention of uric acid stones have been obtained from intermittent administration of Uralyt-U.

Uralyt-U can be taken in courses of a few weeks' duration three times a year or alternatively urine pH can be adjusted by taking Uralyt-U for the first 10 days of each month.

The patient should of course adhere strictly to an appropriate diet and should ensure adequate diuresis.

Follow-up

The response to treatment with Uralyt-U should be supervised by regular visits to the doctor, preferably at intervals of 3 or 4 weeks. At each visit the chart should be scrutinized and the dose corrected if necessary. Other items requiring supervision are body weight, urine deposit and the possibility of urinary infection. It is also advisable to check serum elec-

trolytes (sodium, potassium), uric acid, blood gases and serum creatinine at intervals of approximately 3 months.

COOPERATION BY THE PATIENT (COMPLIANCE)

To ensure the success of treatment of prophylaxis with Uralyt-U, it is essential that the patient should be given a detailed explanation of the correct way to use Uralyt-U and the technique of urine pH measurement. Not until the patient has fully mastered the method of checking treatment and has kept the pH reading within the required range for at least 2 days can he be allowed to manage further medication independently. Since the active constituents of Uralyt-U are stabilized and the dose can hence be measured exactly, this presents no difficulties.

Nearly all patients find that the flavour of Uralyt-U is agreeable. This is an important prerequisite for any medicine which has to be taken regularly over prolonged periods.

Uralyt-U during therapy with uricosuric agents During administration of uricosuric agents there are substantial and sustained increases in urinary uric acid excretion and in some cases it may reach extremely high peak levels. This drug-induced hyperuricosuria may lead to precipitation of uric acid crystals in the renal tubules, and obstruction or formation of uric acid stones are likely complications. In this situation, besides the absolute concentration of uric acid, urine pH and urine dilution are factors which must certainly be given equal weight.

As obstruction of the urinary tract by urates may be entirely symptomless until it causes postrenal anuria, there is good reason for administering Uralyt-U to all patients undergoing uricosuric therapy. The aim is to raise urine pH to levels of between 6.2 and 6.8.

Uralyt-U for patients with cystine stones

Cystinuria is due to a congenital abnormality of the transport mechanisms for cystine and the dibasic amino acids lysine, arginine and ornithine in the kidney and intestine. Reabsorption of these amino acids in the proximal tubule is impaired by a genetic

defect and in consequence their renal clearance is raised. Owing to the abnormality of specific amino acid transport in the small intestinal mucosa, their intestinal absorption is also reduced. However, cystine precursors such as methionine are absorbed in normal amounts.

Cysteine, the reduction product of cystine, is not affected by the abnormality of tubular reabsorption found in patients with cystinuria, and is considerably more soluble in urine than cystine.

Suitable screening tests for detecting cystinuria include the cyanidenitroprusside test and the nickel-sodium dithionite (sodium hydrosulphite) test (Urocystin-Test, Madaus-Diagnostic, Cologne).

Cystine stones are the only form of urinary calculus in which the stone-forming substance is invariably excreted in increased amounts in the urine. In cystine-stone formers the aim of treatment is hence to lower the concentration of cystine in the urine. In such patients urinary cystine concentration is in the supersaturation range and must be brought down into the subsaturation range.

This can be achieved by two therapeutic approaches:

1. By lowering the concentration of cystine in the urine. This can be done by dietary measures and by raising fluid intake (4 litres/day) so as to maintain maximal urinary output throughout the entire day.

2. By enhancing the solubility of cystine.

The physicochemical properties of cystine are responsible for the clinical importance of cystinuria. Above pH 7.6 the solubility of cystine rises steeply.

As it is an amino acid, the pH-dependent solubility of cystine is due to the acidity of its functional groups. For this reason, in addition to urine dilution, alkalinization therapy offers a promising approach. However, urine pH must be maintained above 7 day and night.

The best way of ensuring a pH of 7.5 - 8.0 is to administer Uralyt-U and check urine pH regularly.

The dosage required during the treatment of cystine stones is governed by the response. In principle it

is regulated in the same way as for the treatment of uric acid stones, though higher single or daily doses may be needed. It should be remembered that patients with cystinuria often have a drop in pH at night, and this may call for an extra dose.

For measuring urine pH an indicator paper of appropriate pH range must be used, e.g., pH 7.2 - 9.7 (No. 90211, Macherey & Nage, Duren). Raising the pH to distinctly alkaline levels increases the risk of precipitation of phosphates.

As regards the monitoring of long-term high dosage medication with Uralyt-U in patients with cystinuria, the recommendations previously made for patients with uric acid stones are in general applicable. The possibility of lowering cystine excretion by means of a diet low in methionine and cystine should be remembered.

Oral alkalinizing therapy with Uralyt-U together with raised fluid intake (2-3 litres/day) also seems a logical approach to the treatment of xanthine stones, as xanthine precipitates out only in acid solution. At a pH of around 8.0 the amount of xanthine held in solution is $2^{1/2}$ times greater than at pH 5.8

Uralyt-U and cytostatic therapy

Many of the cytostatic agents used for the chemotherapy of malignant neoplasms carry a risk of nephrotoxic or urotoxic side-effects, but these can sometimes be prevented or minimized by concurrent protective measures. One of the best known of these urotoxic side-effects is the aseptic haemorrhagic cystitis which often complicates the use of oxazaphosphorin cytostatics.

These lesions of the bladder and kidney are attributable to renal elimination of aggressive metabolites in variable concentration in the urine.

There is thought to be some correlation between the aggressiveness of the metabolites and H-ion concentration in the urine. Alkalization with Uralyt-U, started in good time and continued for a sufficient period in conjunction with adequate diuresis, is of considerable value for preventing haemorrhagic complications of the urogenital tract.

Most cytostatic agents or their metabolites are excreted predominantly by the kidney and may cause damage to the tubules. For example, the nephrotoxicity of methotrexate is probably due to precipitation of methotrexate or its metabolites in the renal tubules and collecting tubes, this phenomenon tending to occur in weakly acid solution at a pH of 5.7. By increasing fluid intake and alkalinizing the urine precipitation of methotrexate metabolites in the tubules can be prevented and the kidney can hence be protected against them. Without nephro-protective measures such as alkalinization of the urine, increased fluid intake and other forms of adjuvant therapy (leucovorin), high dosage methotrexate therapy would be extremely hazardous.

When administering Uralyt-U in conjunction with cytostatic therapy the urine pH should be maintained at 7.0 or above so as to provide adequate protection against urotoxic or nephrotoxic side-effects.

Uralyt-U in porphyria cutanea tarda

Because of an abnormality of decarboxylation, patients with porphyria cutanea tarda excrete large amounts of porphyrins, in particular uroporphyrins and heptaporphyrins. As the pK value rises in parallel with the number of acid groups on the porphyrin molecule, the solubility of porphyrins with numerous carboxyl groups is enhanced at alkaline pH levels. Coproporphyrin, for instance, dissociates to a greater extent and is more soluble at pH 7.4 than at pH 5. Alkalization of the urine hence causes it to be excreted in increased amounts, whereas at pH 5, because of its better fat solubility, it tends to be reabsorbed.

Metabolic alkalinization is a form of symptomatic long-term therapy having the objective of first increasing and later decreasing porphyrin excretion. The theoretical rationale for this adjuvant therapy is based on the fact that production of alkaline urine averts back diffusion of coproporphyrin through the renal tubule and hence raises coproporphyrin clearance.

The increase in coproporphyrin excretion is believed

to enhance the synthesis of coproporphyrin from uroporphyrinogen and is therefore accompanied by a fall in circulating uroporphyrin.

This means that metabolic alkalinization should also exert some influence on uroporphyrinogen decarboxylase.

The severity of the uroporphyrinogen-decarboxylase defect in the liver is in linear relation to the accumulation of uroporphyrin and heptacarboxyphyrin in the liver tissue, but inversely proportional to the fraction of excreted coproporphyrin in the urine. Metabolic alkalinization is stated to stimulate porphyrin excretion to such an extent that the rate of elimination exceeds the rate at which it is synthesized. There is also reason to believe that the mechanism of action of metabolic alkalinization in the chronic hepatic porphyrias acts not only on the synthesis shunt uro-coproporphyrinogen, but also directly affects the accumulation of uroporphyrin and heptacarboxyphyrin in the tissues, above all in the liver, owing to the improvement in solubility, which is pH-dependent.

This means that porphyrins deposited in the tissues can be mobilized, while newly synthesized porphyrins will remain in solution and can be excreted.

The essential prerequisites for success are metabolic alkalinization, effected by regular and systematic administration of Uralyt-U so as to keep urine pH between 7.0 and 7.4, and a daily fluid intake of not less than 1.5 l. The objective of treatment is to reduce porphyrin excretion below 1 - 0.5 mg/day. Patients suffering from this disease should strictly avoid alcohol and should not be given female sex hormones (oestrogens).

As a rule, no decline in porphyrin excretion can be expected until 20 days have elapsed since starting to take Uralyt-U.

Metabolic alkalinization with Uralyt-U can be combined with other forms of medical treatment (e.g., chloroquine therapy) for the symptomatic treatment of PCT. Metabolic alkalinization has been claimed to achieve improvement in symptoms, decrease in porphyrin excretion or both in some 85% of patients treated.

Contraindications

Uralyt-U should not be used in patients with acute or chronic renal failure, or when sodium chloride is totally forbidden. It is also contraindicated in patients with serious disorders of acid-base balance (metabolic alkalosis) or chronic urinary tract infections with urea-splitting bacteria.

Interactions with other drugs

If the patient is concurrently taking digitalis, the physician must bear in mind that the normal daily dose of Uralyt-U (10 g of granules) contains approximately 1.75 g (44.8 mmol) of potassium. When prescribing a low sodium diet the physician should remember that the normal daily dose of Uralyt-U contains approximately 1 g (43.5 mmol) of sodium.

Side effects

No side-effects have so far been reported.