Lithoren®

1. General information

1.1. Kidney stones: a). Calcium stones: 75-80% of urinary stones are composed of calcium oxalate and calcium phosphate salts[1-3]. Over-saturation of urine with insoluble calcium salts is the single most important determinant of lithogenesis[1-3]. When concentration of calcium complexes in urine exceeds their solubility the excess salt formed is unable to dissolve. The insoluble salt can precipitate giving rise to calcium oxalate and calcium phosphate crystals[1-3]. Crystals can gradually aggregate and finally form urinary stones[1-3]. **b). Uric acid stones:** 10-12% of urinary stones are composed of uric acid[1-3]. Uric acid stones form in urine usually of low pH and reduced volume. Hyperuricosuria, low pH and low urine volume are the critical elements for the formation of uric acid stones. Alkalization of urine is mandatory[1-3] for the dissolution of uric acid stones. The pH should be increased to a level above 6.5 and the general recommendation is to maintain a pH in the range of 7,0-7,2.

1.2. Metabolic disorders predisposing to urolithiasis: a) Hypocitraturia: Is defined as urine citrate excretion <320mg per day. Low levels of urine citrate is a well known risk factor for calcium stones[4-5]. Hypocitraturia is an ordinary urinary abnormality occurring in 20-60% of patients with calcium stones[5]. Urine citrates are generally regarded as potent inhibitors of calcium stones[1-3]. Citrates act through several mechanisms. By forming water-soluble complexes with urinary calcium ions, thus preventing the over saturation of urine with insoluble calcium oxalate and calcium phosphate complexes. By inhibiting the aggregation and growth of calcium oxalate and calcium phosphate crystals through electrostatic repulsion of oxalate and phosphate anions on the surface of the crystals. **b) Hypercalciuria:** Is defined as daily excretion of urine calcium >300mg for men and >250mg for women while on unrestricted diet. Is the most common urinary abnormality in patients with calcium stones (30-60% of patients with calcium stones)[6]. **c) Hyperoxaluria:** Is defined as urine oxalate excretion >40mg per day. Is an ordinary urinary abnormality in patients with calcium stones (30-35% of patients with calcium stones)[6]. Urinary oxalate is the single stronger promoter of kidney stone formation. One gram of urinary oxalate is 10 times more potent promoter of kidney stone formation than one gram of urinary calcium[7]. Some degree of excessive urinary oxalate is found in 20-30% of all patients with recurrent calcium oxalate stones. Hypercalciuria and hyperoxaluria are the two most important risk factors for calcium oxalate stone formation. Pyridoxine is recommended[1-3] for the management of primary hyperoxaluria. Clinical trials[8-10] have shown that doses of pyridoxine between 10 to 100mgs per day can effectively reduce urinary oxalate excretion in patients with idiopathic hyperoxaluria. **d) Hypomagnesiuria:** Is defined as urine magnesium excretion <72mg per day. Hypomagnesiuria is found in 20% of patients with calcium stones[1-2]. Urinary magnesium is widely acknowledged as a potent inhibitor of calcium urolithiasis[1-3]. Magnesium ions reduce oversaturation of urine with calcium oxalate, through formation of water-soluble magnesium oxalate, and inhibit calcium phosphate and brushite crystal formation[1-3]. **e) Urine acidity:** A pathological urine acidity may induce the formation of uric acid (too acidic urine, i.e. pH<6,2) or calcium phosphate crystals (too alkaline urine, i.e. pH>6,8). Also, It is well known that calcium oxalate stones form **exclusively** over uric acid or calcium phosphate crystals through a process called heterogeneous nucleation[4, 11]. Increased urine acidity is a common finding in patients with uric acid stones. Also, disrupted ability of the kidneys to properly acidify urine is a common finding in patients with renal tubular acidosis.

2. Lithoren®

2.1. What is Lithoren® and what it contains: Lithoren® is a food for special medical purposes (FSMP) that contains potassium citrate, magnesium citrate and pyridoxine as the ingredients with physiological action. Lithoren® is also a urine alkalizer, causing a dose dependent increase of urine pH. **Lithoren®** does not contain sodium.

2.2. Qualitative and quantitative composition: *Ingredients with physiological action:* Each sachet of **Lithoren®**

contains: 2,7gr potassium citrate (25mEq of potassium and 25mEq of citrate ions) (RDA of potassium=2gr), 376mg magnesium citrate (5mEq of magnesium and 5mEq of citrate ions) (RDA of magnesium=300mg), 810mg of citric acid (12mEq of citrate ions) and 25mg of pyridoxine (RDA of pyridoxine=1,5mg). *Inactive ingredients:* sucralose, orange flavor, silicon dioxide.

2.3. Indicated uses: Under medical supervision **Lithoren**® can be used in the dietetic management of some of the most common metabolic disorders that predispose to kidney stones: **1). Lithoren**® can be used in the dietetic management of low urine citrate **(hypocitraturia)**, as it contains citrates. **2). Lithoren**® can be used in the dietetic management of high urine oxalate **(hyperoxaluria)** as it contains pyridoxine. **3). Lithoren**® can be used in case of high urine calcium excretion **(hypercalciuria)** because citrates are known for their ability to complex urine calcium. **4). Lithoren**® can be used in the dietetic management of low urine magnesium **(hypomagnesiuria)** as it contains magnesium. **5). Lithoren**® as an urine alkalizer can be used in the normalization of urine pH, in cases of increased urine acidity. Increased urine acidity is a common finding in patients with uric acid stones. Also, disrupted ability of the kidneys to properly acidify urine is a common finding in patients with renal tubular acidosis.

2.4. Dosage: The dosage of **Lithoren**® should be 1-3 sachets per day, one or two in the evening and one in the morning. Urine pH should be adjusted and regularly monitored to remain within the normal limits (6,2 to 6,8) or even higher (7,0 to 7,2) according to doctor's advise and the degree of the underlying metabolic disorder.

2.5. Administration: The content of each sachet is dissolved in 150mL of water. The resulting solution is clear, orange colored, with a pleasant orange flavor. Stored in the refrigerator (2-8^{o}C), a solution of **Lithoren**® is stable for at least 24h. **Lithoren**® contains sucralose, a zero calories sweetener, so it can be safely administered to diabetics.

2.6. Assessment of urine pH: The package of **Lithoren**® contains novel pH strips for the accurate assessment of urine pH. The most representative assessment is carried out with the **second micturition after morning awakening**[11-14]. For optimum results, a second pH assessment should be performed within the day, preferably in the evening, before going to bed and at least 3hrs after dinner or consumption of coffee, tea, carbonated drinks, wine or beer since food and certain drinks strongly affect urine pH level. This follow-up assessment intends at providing around the clock adequate control of urine pH within normal limits (6,2 to 6,8 or higher).

2.7. Avoid its use: In patients with (or with conditions predisposing to) hyperkalemia. Such conditions include chronic heart or renal failure, uncontrolled diabetes mellitus, acute dehydration (e.g. due to diarrhea or strenuous physical exercise in unconditioned individuals). **Lithoren**® should not be taken together with potassium-sparing diuretics (amiloride/Frumil®, spironolactone/Aldactone®, eplerenone/Inspra®). In patients with active urinary tract infection with either urea-splitting or other organisms, in association with either calcium or struvite stones.

2.8. Precautions: Hyperkalemia: Normal serum potassium levels range between 3,5 and 5,0mEq/L. Mild hyperkalemia is often asymptomatic and easily treated[15]. Periodic blood tests of potassium levels are recommended in patients using **Lithoren**® when at risk of developing hyperkalemia.

2.9. Side effects: During dietetic management of **Lithoren**® some patients may develop minor gastrointestinal complaints. These may be alleviated by taking the dose with meals or snacks or by reducing the dose.

2.10. Pregnancy: Category C. There are no human or animal studies whether **Lithoren**® can cause fetal harm when administered to pregnant women or can affect reproduction capacity. **Lithoren**® should be given to pregnant women only if clearly needed.

2.11. Caution: **Lithoren**® is to be used under medical supervision in the dietetic management of patients who have a disrupted ability to excrete normal quantities of certain minerals in urine or in patients who have a disrupted ability to properly acidify urine. **Lithoren**® does not prevent, treat or cure a human disease. Do not exceed the highest recommended daily dose. Keep out of children's reach. Store at room temperature (15-30^{o}C) and avoid contact of the product with water, heat radiators or its direct exposure to sunlight. Potassium cit-

rate is hygroscopic. In case of absorption of moisture, lumps can form inside the sachets. This is a natural event not affecting the efficacy of **Lithoren®**. Do not use the product beyond the expiration date indicated on the outer package.

2.12. Packaging: Carton box with 30 sachets of **Lithoren®.** The package also includes a patient information leaflet and a clear plastic zip-lock envelope containing 14 pH strips, a color matching chart with pH values between 4,50 and 9,00 and a desiccant.

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