SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Urever 20 mg/2 mL I.M./I.V. Ampoule Containing Solution

Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:

Furosemide 20 mg

Excipients:

Sodium chloride 15 mg

Sodium hydroxide 2.56 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

Clear, colorless solution in an amber glass ampoule

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Fluid retention associated with chronic congestive heart failure (if diuretic therapy is required),
- Fluid retention associated with acute congestive heart failure
- Fluid retention associated with chronic renal impairment,
- Maintaining fluid excretion in acute renal impairment, including due to pregnancy or burns.
- Fluid retention associated with nephrotic syndrome (if diuretic therapy is required),
- Fluid retention associated with liver disease (if treatment with aldosterone antagonists needs to be supported),
- Hypertension,
- Hypertensive crisis (as a supportive measure),
- Forced diuresis support.

4.2. Posology and method of administration

Posology/ Administration frequency and duration:

The lowest dose sufficient to achieve the desired effect should be used.

Furosemide is given intravenously only when oral administration is not possible or effective (eg, intestinal malabsorption) or if rapid action is required. If intravenous therapy is used, it is recommended to switch to oral therapy as soon as possible.

Continuous infusion of furosemide is generally preferred over repeated bolus injections to achieve optimal efficacy and suppress counter-regulation. When continuous infusion of furosemide cannot be used for follow-up treatment after one or more acute bolus doses, a follow-up regimen of low doses at short intervals (approximately 4 hours) should be preferred over a regimen of high bolus doses at long intervals.

The maximum recommended daily dose of furosemide for both intravenous and oral administration in adults is 1500 mg.

The duration of treatment varies according to the indication and is determined by the physician on an individual patient basis.

Method of administration:

Intravenous injection/infusion:

Intravenous furosemide should be administered by slow injection or infusion, not to exceed 4 mg/minute. In patients with severe renal dysfunction (serum creatinine > 5 mg/dL), it is recommended not to exceed an infusion rate of 2.5 mg/min.

Intramuscular injection:

Intramuscular administration should be limited to exceptional cases where oral or intravenous administration is not possible. It should be noted that intramuscular injection is not suitable for the treatment of acute diseases such as pulmonary edema.

UREVER should not be mixed with other drugs in the syringe.

UREVER is a solution with a pH value of about 9 without buffering capacity. Therefore, the active substance may precipitate at pH values below 7. However, if this solution is to be diluted, care should be taken to ensure that the pH of the diluted solution is in the weak alkaline to neutral range.

Normal saline solution is suitable as the diluent. It is recommended to use diluted solutions immediately.

Additional information for special populations

Renal Impairment:

Fluid retention associated with chronic renal impairment:

The natriuretic response to furosemide varies depending on many factors, such as the degree of renal impairment and sodium balance, and therefore it is not possible to fully predict the effect of a dose. In patients with chronic renal impairment, the dose should be carefully titrated so that the initial fluid loss is gradual. For adults, it is a dose that results in a loss of approximately 2 kg of body weight (about 280 mmol Na^+) per day.

The recommended oral starting dose is 40 mg - 80 mg per day. This dose can be adjusted according to response as needed. The total daily dose can be given as a single dose or in two divided doses.

In dialysis patients, the usual maintenance oral dose is 250 mg to 1500 mg daily.

In intravenous therapy, the dose of furosemide can be determined by starting with a continuous intravenous infusion of 0.1 mg/minute and then gradually increasing the infusion rate every half hour according to response.

Maintaining fluid excretion in acute renal impairment:

Hypovolemia, hypotension, and significant electrolyte and acid-base imbalance should be corrected before starting furosemide. It is recommended to switch from the intravenous route to the oral route as soon as possible.

The recommended starting dose is 40 mg, given as an intravenous injection. If this dose does not produce the desired increase in fluid excretion, furosemide may be given by continuous intravenous infusion starting at a rate of 50 mg-100 mg/hr.

Fluid retention associated with nephrotic syndrome:

The recommended oral starting dose is 40 mg - 80 mg per day. This dose can be adjusted according to response as needed. The total daily dose can be given as a single dose or in several divided doses(see section 4.4).

Hepatic Impairment:

Fluid retention associated with liver disease

Furosemide is used to support treatment with aldosterone antagonists in cases where aldosterone antagonists alone are insufficient. To avoid complications such as orthostatic intolerance or electrolyte and acid-base imbalances, the dose should be carefully titrated so that the initial fluid

loss is gradual. For adults, this means a dose that results in a body weight loss of about 0.5 kg per day.

The recommended oral starting dose is 20 mg - 80 mg per day. This dose can be adjusted according to response as needed. The daily dose can be given as a single dose or in divided doses. If intravenous therapy is absolutely necessary, the initial single dose is 20 mg - 40 mg.

Others

Fluid retention associated with chronic congestive heart failure

The recommended oral starting dose is 20 mg - 80 mg per day. This dose can be adjusted according to response as needed. It is recommended that the daily dose be given in two or three divided doses.

Fluid retention associated with acute congestive heart failure

The recommended oral starting dose is 20 mg to 40 mg given by intravenous bolus injection. This dose can be adjusted according to response as needed.

Hypertension

Furosemide can be used alone or in combination with other antihypertensive agents.

The usual maintenance oral dose is 20 mg - 40 mg per day. Higher doses may be required in hypertension associated with chronic renal failure.

Hypertensive crisis

The recommended starting dose is 20 mg- 40 mg, given as an intravenous injection. This dose can be adjusted according to response as needed.

Forced diuresis support in poisoning

Furosemide is given intravenously in addition to infusions of electrolyte solutions. Dosage varies with response to furosemide. Fluid and electrolyte losses should be corrected before and during treatment. In case of poisoning with acid or alkaline substances, elimination can be further increased by alkalization or acidification of the urine, respectively.

The recommended starting dose is 20 mg - 40 mg, given by intravenous injection.

Pediatric population:

In children, the recommended dose of furosemide for oral administration is 2 mg/kg body weight up to a maximum daily dose of 40 mg. The recommended dose of furosemide for parenteral administration is 1 mg/kg body weight up to a maximum daily dose of 20 mg.

In children, the dosage should be reduced according to body weight. For maximum doses in children, see "Posology/frequency of administration".

Geriatric population:

Dose adjustment should be done with caution in elderly patients with dementia.

4.3. Contraindications

UREVER must not be used in the following cases:

- In patients with hypersensitivity to furosemide or any of the excipients of UREVER. Patients allergic to sulfonamides (e.g. sulfonamide antibiotics or sulfonylureas) may be cross-sensitive to furosemide.
- In patients with hypovolemia or dehydration.
- In patients with anuric renal failure unresponsive to furosemide.
- In patients with severe hypokalemia.
- In patients with severe hyponatremia.
- In patients with pre-comatous and comatose conditions associated with hepatic encephalopathy.
- In breast-feeding women.

For use during pregnancy, see section 4.6

4.4. Special warnings and special precautions for use

Urine output must be ensured. Patients with partial urinary outflow obstruction (e.g., patients with bladder emptying disorder, prostatic hyperplasia, or urethral narrowing) may cause or exacerbate complaints by increased urine production. Therefore, these patients require careful monitoring, especially during the initial stages of treatment.

Treatment with UREVER requires regular medical supervision. Careful monitoring is required in the following situations:

- In patients with hypotension,
- In patients in whom a significant drop in blood pressure would be particularly at risk, e.g.

patients with significant stenosis of the coronary arteries or blood vessels supplying the brain,
- In patients with latent or manifest diabetes mellitus,
- In gout patients,
- Hepatorenal syndrome, i.e. in patients with functional renal failure associated with severe liver disease,
- Careful dose titration is required in patients with hypoproteinemia (e.g. in association with the nephrotic syndrome (furosemide may weaken and its ototoxicity may increase).
- In premature babies (possible development of nephrocalcinosis/nephrolithiasis; kidney functions should be followed, ultrasonography should be applied.)

Monitoring of serum sodium, potassium and creatinine is generally recommended during furosemide therapy. Particularly close monitoring is required in patients at high risk of developing electrolyte imbalances or in the event of significant additional fluid loss (e.g. due to vomiting, diarrhea or excessive sweating). Significant electrolyte and acid-base imbalances, as well as hypovolemia and dehydration, should be corrected. This may require temporary discontinuation of furosemide therapy.

Concomitant use with risperidone:
In placebo-controlled studies of risperidone in elderly patients with dementia, patients treated with furosemide alone (aged 67-90 years, mean 80 years; 4.1%) or patients treated only with risperidone (aged 70-96 years, mean 84 years; %). 3.1), an increased incidence of mortality was observed in patients treated with furosemide and risperidone (aged 75-97 years, mean age 89 years; 7.3%). Concomitant use of risperidone with other diuretics (especially low-dose thiazide diuretics) is not associated with similar findings.

There is no pathological mechanism explaining this finding and no consistent cause of death. However, appropriate precautions should be taken and the risk and benefit of this combination or of concomitant therapy with other effective diuretics should be considered primarily when deciding on use. There was no increase in the incidence of mortality in patients with concomitant use of risperidone and other diuretics. Regardless of treatment, dehydration is a high risk factor for mortality and therefore caution should be exercised in elderly patients with dementia.

In the event of anaphylactic shock, the following immediate precautions are generally recommended:

When the first symptoms such as sweating, nausea, cyanosis appear, the injection is stopped immediately. The needle is left in the vein or a suitable cannula is inserted into the vein to keep the vascular access open. Along with other precautions taken as usual, the patient is laid with his head down and the airways are kept open.

Medications to be administered immediately:

Administer epinephrine (adrenaline) immediately by the I.V. route:
1 mL of a commercially available 1/1000 epinephrine solution is diluted to 10 mL, and 1 mL of this (0.1 mg epinephrine) is injected slowly by controlling the pulse and blood pressure (beware of rhythm disturbances!). Epinephrine injections may be repeated if necessary (see patient information leaflet).

Glucocorticoids such as 250-1000 mg methylprednisolone-21-hydrogen succinate are then administered intravenously. Repeat doses of glucocorticoids if necessary (see leaflets for these drugs).

Subsequently, **volume substitution** is made by using solutions such as plasma expander, Human-albumin, and full electrolyte solution via **I.V.**

Other treatment precautions:
Artificial respiration, inhalation of oxygen, administration of calcium and antihistamines. A pre-existing metabolic alkalosis (e.g. in decompensated liver cirrhosis) may worsen during furosemide therapy.

This medicinal product contains less than 1 mmol (23 mg) sodium per "dose"; so it's actually "sodium free".

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

Foods:

Whether and to what extent the absorption of furosemide is affected when taken with food depends on the pharmaceutical formulation.

Not recommended concomitant uses:
In isolated cases, intravenous administration of furosemide within 24 hours after ingestion of chloral hydrate may cause flushing, sweating attacks, discomfort, nausea, increased blood pressure, and tachycardia. Therefore, the concomitant use of furosemide with chloralhydrate is not recommended.

Furosemide may increase the ototoxicity of aminoglycosides and other ototoxic drugs. Because this can cause irreversible damage, these drugs must only be used in combination with furosemide if there are compelling medical reasons.

Precautions for use:

There is a risk of ototoxic effects if cisplatin and furosemide are given concomitantly. In addition, when used to induce forced diuresis during cisplatin therapy, the nephrotoxicity of cisplatin may be increased if furosemide is not given at low doses (e.g. 40 mg in patients with normal renal function) and with positive fluid balance.

Oral furosemide and sucralfate should be used at least 2 hours apart, as sucralfate reduces the intestinal absorption of furosemide and therefore its effect.

Furosemide reduces the excretion of lithium salts and may cause increased serum lithium levels, resulting in an increased risk of lithium toxicity, including an increased risk of cardiotoxic and neurotoxic effects of lithium. Therefore, careful monitoring of lithium levels is recommended in patients receiving this combination.

Patients taking diuretics may experience severe hypotension and worsening of renal function, including cases of renal impairment, especially when an angiotensin converting enzyme inhibitor (ACE inhibitor) or angiotensin II receptor antagonist is given for the first time or for the first time in an increased dose. Consideration must be given to temporarily interrupting furosemide administration or reducing the dose of furosemide for at least 3 days before initiating or increasing the dose of an ACE inhibitor or angiotensin II receptor antagonist.

Risperidone: Appropriate precautions should be taken and the risk and benefit of this combination or of concomitant therapy with other potent diuretics should be considered

primarily when deciding on use (see section 4.4; warnings regarding increased mortality in elderly patients with dementia using risperidone in combination with furosemide).

Points to take into consideration:
Concomitant administration of non-steroidal anti-inflammatory drugs, including acetylsalicylic acid, may reduce the effect of furosemide. In patients with dehydration or hypovolemia, non-steroidal anti-inflammatory drugs can cause acute renal failure.

Furosemide may increase salicylate toxicity.

Weakening of the effect of furosemide may occur following co-administration of phenytoin.

The use of corticosteroids, carbenoxolone, large amounts of licorice and prolonged use of laxatives may increase the risk of developing hypokalemia.

Some electrolyte disturbances (eg, hypokalemia, hypomagnesemia) may increase the toxicity of some other drugs (e.g., digitalis preparations and drugs that cause QT interval prolongation syndrome).

A more significant reduction in blood pressure should be expected if antihypertensive agents, diuretics or other drugs with blood pressure lowering potential are co-administered with furosemide.

Other drugs that undergo significant renal tubular secretion, such as probenecid and methotrexate, may reduce the effect of furosemide.

On the other hand, furosemide can reduce the renal excretion of these drugs. In the case of high-dose therapy (especially high-dose of both furosemide and other drugs), this may lead to increased serum levels and an increased risk of adverse effects from furosemide or the concomitant drug.

The effects of antidiabetic drugs and sympathomimetics that increase blood pressure (e.g., epinephrine, norepinephrine) may be reduced. The effects of curare-type muscle relaxants or

theophylline may be increased.

The harmful effects of nephrotoxic drugs on the kidney may be increased.

Renal dysfunction may develop in patients receiving concomitant treatment with high doses of certain cephalosporins and furosemide.

Concomitant use of cyclosporine A and furosemide is associated with an increased risk of gouty arthritis secondary to furosemide-induced hyperuremia and cyclosporine's impairment of renal urate excretion.

Patients at high risk for radiocontrast nephropathy treated with furosemide had a higher incidence of impaired renal function after receiving radiocontrast compared to high-risk patients who received only intravenous hydration before receiving radiocontrast.

4.6. Pregnancy and lactation

General advice

Pregnancy Category: C

Women with childbearing potential/Birth control (Contraception)

No data are available on use in women of childbearing potential. Animal studies have shown reproductive toxicity. The potential risk for humans is unknown.

Pregnancy

Furosemide crosses the placental barrier. It should not be given during pregnancy unless there are compelling medical reasons. Treatment during pregnancy requires monitoring of fetal growth.

Lactation

Furosemide passes into breast milk and may inhibit lactation. Women treated with furosemide should not breast-feed their infants.

Reproductive ability / fertility

Furosemide did not impair the fertility of male and female rats orally at doses of 90 mg/kg body weight per day and female mice at doses of 200 mg/kg body weight per day.

No significant embryotoxic or teratogenic effects were detected after treatment with furosemide in various mammalian species such as mice, rats, cats, rabbits, and dogs. 7-11 and 14-18 of pregnancy. Delay in kidney maturation—decrease in differential glomeruli count—has been described in the rat generation treated with furosemide 75 mg/kg body weight on the first day of rats.

Furosemide crosses the placental barrier and reaches 100% of maternal serum concentrations in umbilical cord blood. Up to now, no malformations that may be associated with furosemide have been identified in humans. However, insufficient experience has been gained to allow a definitive assessment of possible harmful effects on the embryo/fetus. Urine production in the fetus can be stimulated in the uterus.

Urolithiasis and nephrocalcinosis have been observed following treatment of premature infants with furosemide. No studies have been conducted to evaluate the effects of breast-milk furosemide on the infant.

4.7. Effects on ability to drive and use machines

Some adverse effects (e.g., an undesirably significant drop in blood pressure) may impair the patient's ability to concentrate and react and thus pose a risk in situations where these abilities are particularly important (e.g., driving or using machinery).

4.8. Undesirable effects

Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1000 to <1/100), Rare (≥1/10000 to <1/1000) Very rare (<1/10,00), Unknown (cannot be estimated from the available data.

Metabolic and nutritional diseases

Very common : Electrolyte disturbances (including symptomatic), hypovolemia and dehydration, especially in elderly patients, increased blood creatinine, increased triglyceride serum levels

Common : Hyponatremia, hypochloremia, hypokalemia and increase in blood cholesterol, increase in serum uric acid and gout attacks

Uncommon : Impaired glucose tolerance. In patients with diabetes mellitus, this may lead to

impaired metabolic control; latent diabetes mellitus may manifest.

Unknown : Hypocalcemia, hypomagnesaemia, increased urea in the blood, metabolic alkalosis, Pseudo-Barter syndrome in the context of abuse and/or long-term use of furosemide.

Vascular diseases
Very common (for intravenous administration): Hypotension, including orthostatic hypotension

Rare : Vasculitis

Unknown : Thrombosis

Kidney and urinary tract diseases
Common : increase in urine output

Rare : Tubulointerstitial nephritis

Unknown : Increased urinary sodium, increased urinary chloride, urinary retention (in patients with partial urinary outflow obstruction), nephrocalcinosis/nephrolithiasis/renal failure in premature infants

Gastrointestinal diseases
Not common : Nausea

Rare : Vomiting, diarrhea

Very rare : Acute pancreatitis

Hepatobiliary diseases
Very rare : Cholestasis, increase in transaminases

Ear and inner ear diseases
Uncommon : Hearing impairments, mostly transient, especially in patients with renal failure, hypoproteinemia (e.g. in nephrotic syndrome) and/or when intravenous furosemide is given too rapidly. Cases of deafness, sometimes irreversible, have been reported after oral or I.V. administration of furosemide.

Rare : Tinnitus

Skin and subcutaneous tissue diseases

Not common : Itching, urticaria, rashes, bullous dermatitis, erythema multiforme, pemphigoid, exfoliative dermatitis, purpura, photosensitivity reaction

Unknown : Stevens-Johnson syndrome, toxic epidermal necrolysis, AGEP (acute generalized exanthema pustulous) and DRESS (drug rash with eosinophilia and systemic symptoms)

Immune system diseases

Rare : Severe anaphylactic or anaphylactoid reactions (eg with shock)

Nervous system diseases

Common : Hepatic encephalopathy in patients with hepatocellular insufficiency

Rare : Paresthesia

Blood and lymphatic system diseases

Common : Hemoconcentration

Uncommon : Thrombocytopenia

Rare : Leukopenia, eosinophilia

Very rare : Agranulocytosis, aplastic anemia or hemolytic anemia

Congenital and hereditary/genetic diseases

Unknown : There is an increased risk of persistence of patent *ductus arteriosus* if furosemide is administered to premature infants within the first week of life.

General disorders and administration site conditions

Rare : Fever

Unknown : Local reactions such as pain following intramuscular injection

Reporting of suspected adverse reactions

It is of great importance to report suspicious drug adverse reactions after licensing. Reporting allows you to constantly monitor the benefit/risk balance of the drug. Healthcare professionals are required to report any suspected adverse reactions to the Turkish Pharmacovigilance Center

(TUFAM). (www.titck.gov.tr: e-mail: tufam@titck.gov.tr: tel: 0 800 314 00 08; fax: 0312 218 35 99)

4.9. Overdose and Treatment

Symptoms: In acute or chronic overdose, the clinical picture differs mainly depending on the degree and consequences of electrolyte and fluid loss, eg, hypovolemia, dehydration, hemoconcentration, cardiac arrhythmias (including A-V block and ventricular fibrillation). Symptoms of these disorders include severe hypotension (progressing to shock), acute renal failure, thrombosis, delirium, flaccid paralysis, apathy, and confusion.

Treatment: No specific antidote for furosemide is known. If the ingestion has taken place very recently, an attempt may be made to limit further systemic absorption of the active substance by measures such as gastric lavage or measures designed to reduce absorption (eg, activated charcoal).

Clinically significant disturbances in electrolyte and fluid balance should be corrected. Along with the prevention and treatment of serious complications and other effects on the body resulting from these disorders, this corrective intervention may require general and specific intensive medical monitoring and therapeutic measures.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Loop diuretics

ATC Code: C03CA01

Mechanism of Action:

Furosemide is a loop diuretic that provides relatively potent and short-lived rapid-onset diuresis. Furosemide blocks the Na+K+2Cl- co-transport system located in the luminal cell membrane of the thick ascending limb of the loop of Henle: therefore, the efficacy of the saluretic effect of furosemide is dependent on the drug reaching the tubular lumen via an anion transport mechanism. The diuretic effect is due to the inhibition of sodium chloride reabsorption in this section of the loop of Henle. As a result, functional sodium excretion can reach 35% of glomerular sodium filtration. Secondary effects of increased sodium excretion are increased urinary excretion (due to osmotically bound water) and increased distal tubular potassium secretion. The excretion of calcium and magnesium ions also increases.

Furosemide interrupts the tubulo-glomerular feedback mechanism in the macula densa, with the result that there is no reduction in saluretic activity. Furosemide causes dose-dependent stimulation of the renin-angiotensin-aldosterone system.

In heart failure, furosemide causes an acute reduction in cardiac pre-load (by diluting venous capacitance vessels). This early vascular effect is thought to be mediated by prostaglandin and require adequate renal function through activation of the renin-angiotensin system and intact prostaglandin synthesis. In addition, due to its natriuretic effect, furosemide reduces the increased vascular reactivity to catecholamines in hypertensive patients.

The antihypertensive efficacy of furosemide may be attributed to increased sodium excretion, decreased blood volume, and decreased sensitivity of vascular smooth muscle to vasoconstrictor stimuli.

Pharmacodynamic properties

The diuretic effect of furosemide is seen within 15 minutes of an intravenous dose and within 1 hour of an oral dose.

A dose-dependent increase in diuresis and natriuresis has been demonstrated in healthy subjects receiving furosemide at doses of 10 mg to 100 mg. In healthy subjects, the duration of action is approximately 3 hours after an intravenous dose of 20 mg of furosemide and 3-6 hours after an oral dose of 40 mg.

In patients, the relationship between intratubular concentrations of unbound (free) furosemide (estimated using the urinary furosemide excretion rate) and its natriuretic effect is in the form of a sigmoid curve, with a minimal effective excretion rate of furosemide of approximately 10 micrograms/min. Therefore, continuous infusion of furosemide is more effective than repeated bolus injections. In addition, above a certain bolus dose of the drug, there is no significant increase in the effect. The effect of furosemide is reduced if tubular secretion of the drug or intra-tubular albumin binding is decreased.

5.2. Pharmacodynamic properties

General properties

Absorption:

Furosemide is rapidly absorbed from the gastrointestinal tract. Absorption of the drug shows wide inter-individual and intra-individual variability. The bioavailability of furosemide in

healthy volunteers is approximately 50%-70% for tablets and 80% for oral solution. In patients, the bioavailability of the drug is affected by a variety of factors, including underlying disease, and may be as low as 30% (eg, in nephrotic syndrome).
Whether and to what extent the absorption of furosemide is affected when taken with food depends on the pharmaceutical formulation.

Distribution:
The volume of distribution of furosemide is 0.1 - 0.2 liters per kg body weight. The volume of distribution may be higher depending on the underlying disease.

Furosemide is strongly (over 98%) bound to plasma protein, mainly to albumin.

Biotransformation:
Between 10% and 20% of the reclaimed substances in the urine consists of a glucuronide metabolite of furosemide.

Elimination:
Elimination of furosemide occurs as largely unchanged drug, mainly by secretion into the proximal tubule. After intravenous administration, 60% to 70% of the furosemide dose is excreted by this route. The remaining dose is excreted in the faeces, presumably following bile secretion.

The terminal half-life of furosemide after intravenous administration is approximately 1 - 1.5 hours.

Furosemide is excreted in breast milk. Furosemide crosses the placental barrier and is slowly transported to the fetus. It is present in the fetus or newborn baby in the same concentration as the mother.

Characteristics in patients

Renal/ Hepatic impairment

In renal failure, the elimination of furosemide is slowed and its half-life is prolonged; In patients with severe renal impairment, the terminal half-life may reach 24 hours.

Decreased plasma protein concentration in nephrotic syndrome leads to higher unbound (free) furosemide concentration. On the other hand, the efficacy of furosemide is reduced in these patients due to intratubular albumin binding and decreased tubular secretion.

Furosemide is dialyzable at low levels in patients undergoing hemodialysis, peritoneal dialysis,

and CAPD.

In hepatic failure, the half-life of furosemide is increased by 30-90%, mainly due to a larger volume of distribution. In addition, there is wide variation in all pharmacokinetic parameters in this patient group.

Congestive heart failure, severe hypertension and geriatric population:
In patients with congestive heart failure, severe hypertension, or the elderly, elimination of furosemide is slowed due to decreased renal function.

Premature and term babies:
Depending on the maturity of the kidney, the elimination of furosemide may be slowed. If the baby's glucuronizing capacity is impaired, the metabolism of the drug also slows down.
The terminal half-life is less than 12 hours in infants older than 33 weeks after conception. In infants two months of age and older, terminal clearance is the same as in adults.

5.3. Preclinical safety data

Acute toxicity:
Studies with oral and intravenous administration of furosemide in various rodent species and dogs have revealed low rates of acute toxicity. The LD_{50} of furosemide is between 1050 - 4600 mg/kg body weight in mice and rats and 243 mg/kg body weight in guinea pigs. In dogs, the oral LD_{50} is about 2000 mg/kg body weight and the I.V. LD_{50} is more than 400 mg/kg body weight.

Chronic toxicity:
After 6 and 12 months of administration in rats and dogs, renal changes (including focal fibrosis, calcification) were seen at the highest dosage groups (10-20 times the therapeutic dose in humans).

Ototoxicity:
Furosemide can inhibit transport processes in the stria vascular of the inner ear, possibly leading to (usually reversible) hearing impairment.

Carcinogenicity:
Furosemide was administered to female mice and rats in their diet at an amount of approximately 200 mg/kg body weight (14,000 ppm) per day for approximately 2 years. An increased incidence of mammary adenocarcinoma was observed in mice, but not in rats. This

dose is considerably higher than the therapeutic dose administered in humans. Furthermore, these tumors are morphologically identical to the spontaneously occurring tumors observed in 2% to 8% of control animals.

It is therefore unlikely that this incidence of tumors is applicable to the treatment of humans. Indeed, there is no evidence of an increased incidence of human breast adenocarcinoma following the use of furosemide. Based on epidemiological studies, a carcinogenicity classification for furosemide in humans is not possible.

In a carcinogenicity study, furosemide was administered to rats at doses of 15 and 30 mg/kg body weight per day. Male rats in the 15 mg/kg dose category (but not in the 30 mg/kg dose category) showed a marginal increase in rare tumors. These findings are considered to be accidental.

Nitrosamine-induced bladder carcinogenesis in rats did not provide any evidence that furosemide is an accelerating factor.

Mutagenicity:
In vitro tests on bacteria and mammalian cells have yielded both positive and negative results. However, induction of gene and chromosomal mutations has only been observed when furosemide reaches cytotoxic concentrations.

Reproductive toxicology:
Furosemide did not impair the fertility of male and female rats orally at doses of 90 mg/kg body weight per day and female mice at doses of 200 mg/kg body weight per day.

No significant embryotoxic or teratogenic effects were detected after treatment with furosemide in various mammalian species such as mice, rats, cats, rabbits, and dogs. 7-11 and 14-18 of pregnancy. Delay in kidney maturation—decrease in differential glomeruli count—has been described in the rat generation treated with furosemide 75 mg/kg body weight on the first day of rats.

Furosemide crosses the placental barrier and reaches 100% of maternal serum concentrations in umbilical cord blood. Up to now, no malformations that may be associated with furosemide have been identified in humans. However, insufficient experience has been gained to allow a definitive assessment of possible harmful effects on the embryo/fetus. Urine production in the

fetus can be stimulated in the uterus.

Urolithiasis and nephrocalcinosis have been observed following treatment of premature infants with furosemide.

No studies have been conducted to evaluate the effects of breast-milk furosemide on the infant.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium chloride

Sodium hydroxide (for pH adjustment)

Water for injection

6.2. Incompatibilities

Not applicable

6.3. Shelf Life

24 months

6.4. Special precautions for storage

Store at room temperature between 15-30°C.

6.5. Nature and contents of container

UREVER is available in packages containing 5 ampoules or 100 ampoules of 2 mL (=20 mg).

6.6. Instructions for use and handling and disposal

Unused products or waste materials should be disposed of in accordance with the "Medical Waste Control Regulation" and Packaging Waste Control Regulations.

7. MARKETING AUTHORIZATION HOLDER

OSEL İlaç Sanayi ve Ticaret A.Ş.
Akbaba Mah. Maraş Cad. No:52
Beykoz/İSTANBUL

8. MARKETING AUTHORIZATION NUMBER

240/81

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORISATION

First authorization date: 13.10.2004

License renewal date: 20.11.2009

10. DATE OF OF REVISION OF THE TEXT