SUMMARY OF PRODUCT INFORMATION

1. Name of the medicinal product

DESAL® 20 mg/2 ml IM/IV Solution for Injection.

2. Qualitative and quantitative composition

Active ingredient:

Furosemide 20 mg

Excipients:

Sodium hydroxide	3 mg
Sodium chloride	14 mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Sterile injection solution. Clear, very light yellow solution

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 with renal failure,
- The maintenance of fluid excretion in acute renal failure. including due to pregnancy or burns,
- Fluid retention associated with nephrotic syndrome (if diuretic therapy is required),
- Fluid retention associated with liver disease (if necessary to supplement treatment with aldosterone antagonists),
- Hypertension,
- Hypertensive crisis (as supportive measures),
- Support of forced diuresis.

4.2 Posology and method of administration

Posology / application frequency and duration

This therapy should be titrated to gain maximal therapeutic response with the minimum dose possible.

Furosemide is given intravenously only when oral administration is not feasible or is ineffective (Eg. In the intestinal absorption disorder) or if rapid effect is required. If intravenous therapy is used, it is recommended that transfer to oral therapy be carried out as soon as possible.

To achieve optimum efficacy and suppress counter-regulation, a continuous furosemide (frusemide) infusion is generally preferred to repeated bolus injections.
Where continuous furosemide infusion is not feasible for follow-up treatment after one or several acute bolus doses, a follow-up regimen with low doses given at short intervals (approx. 4 hours) is to be preferred to a regimen with higher bolus doses at longer intervals.

In adults, the maximum recommended daily dose of furosemide for both intravenous and oral administration 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 must be injected or infused slowly; a rate of 4 mg per minute must not be exceeded. In patients with severe impairment of renal function (serum creatinine>5 mg/dl), it is recommended that an infusion rate of 2.5 mg per minute is not exceeded.

Intramuscular injection:
Intramuscular administration must be restricted to exceptional cases where neither oral nor intravenous administration are feasible. It must be noted that intramuscular injection is not suitable for the treatment of acute conditions such as pulmonary oedema.

DESAL should not be mixed with other medicines in same syringes.

DESAL is a solution with a pH of about 9, without buffering capacity. Therefore, the active substance can precipitate at pH values below 7. Therefore, if this solution is to be diluted, it should be noted that the pH of the diluted solution is in the weak alkaline to neutral range. Normal saline solution is suitable as diluent. It is recommended to use diluted solutions as soon as possible.

Additional information on special populations

Renal impairment:
Fluid retention associated with chronic renal failure:
The natriuretic response to furosemide depends on a number of factors, including severity of renal failure and the sodium balance, and, therefore, the effect of a dose cannot be accurately predicted. In patients with chronic renal failure, the dose must be carefully titrated so that the initial loss of fluid is gradual. For adults, this means a dose which leads to a loss of approx. 2 kg body weight (approx. 280 mmol Na+) per day.
The recommended initial oral dose is 40 mg to 80 mg daily. This may be adjusted as necessary according to response. The total daily dose may be given as a single dose or two divided doses. In dialysis patients, the usual oral maintenance dose is 250 mg to 1500 mg daily.
In intravenous treatment, the dose of furosemide may be determined by starting with a continuous intravenous infusion of 0.1 0.1 mg / min and then gradually increasing the rate every half hour according to response.

Maintenance of fluid excretion in acute renal failure:
Hypovolaemia, hypotension, and significant electrolyte and acid-base imbalances must be corrected before starting furosemide. It is recommended that transfer from the intravenous to the oral route of administration is carried out as soon as possible.

The recommended initial dose is 40 mg given as an intravenous injection. If this does not lead to the desired increase in fluid excretion, furosemide may be given as a continuous intravenous infusion, starting with a rate of 50 mg to 100 mg per hour.

Fluid retention associated with nephrotic syndrome:
The recommended initial oral dose is 40 mg to 80 mg daily. This may be adjusted as necessary according to response. The total daily dose may be given as a single dose or several divided doses. See section 4.4

Hepatic failure:
Fluid retention associated with liver disease:
Furosemide is used to supplement treatment with aldosterone antagonists in cases where these alone are not sufficient. In order to avoid complications such as orthostatic intolerance or electrolyte and acid-base imbalances, the dose must be carefully titrated so that the initial loss of fluid is gradual. For adults, this means a dose which leads to a loss of approx. 0.5 kg body weight per day.
The recommended initial oral dose is 20 mg to 80 mg daily. This may be adjusted as necessary according to response. The daily dose may be given as a single dose or divided doses. If intravenous treatment is absolutely necessary, the initial single dose is 20 mg to 40 mg.

Other:
Fluid retention associated with chronic congestive cardiac failure
The recommended oral initial dose is 20 mg - 80 mg per day. This dose can be adjusted according to the response. It is recommended that the daily dose be administered in two or three divided doses.
Fluid retention associated with acute congestive cardiac failure
The recommended initial dose is 20 to 40 mg given as an intravenous bolus injection. The dose may be adjusted as necessary according to response.

Hypertension
Furosemide can be used alone or in combination with other antihypertensive agents.
The usual oral maintenance dose is 20 mg to 40 mg daily. In hypertension associated with chronic renal failure, higher doses may be required.

Hypertensive crisi

The recommended initial dose of 20 mg to 40 mg is given as an intravenous bolus injection. This may be adjusted as necessary according to response.

Support of forced diuresis in poisoning

Furosemide is given intravenously in addition to infusions of electrolyte solutions. The dose is dependent on the response to furosemide. Fluid and electrolyte losses must be corrected before and during treatment.
In case of poisoning with acid or alkaline substances, elimination can be increased further by alkalisation or acidification respectively, of the urine.
The recommended initial dose is 20 mg to 40 mg given intravenously.

Children:
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 dosage is to be reduced in relation to body weight.
For maximum doses in children, see under the heading "Posology / frequency of administration".

Geriatric population:
Dose adjustment should be done carefully in elderly patients with dementia.

4.3 Kontrendikasyonlar

DESAL should not be used in the following cases:

- İn patients with hypersensitivity to furosemide or any of the excipients of DESAL. Patients allergic to sulfonamides (e.g. sulfonamide antibiotics or sulfonylureas) may show cross-sensitivity to furosemide.
- in patients with hypovolaemia or dehydration.
- in patients with anuric renal failure not responding to furosemide.
- in patients with severe hypokalaemia.
- in patients with severe hyponatraemia.
- in patients with pre-comatose and comatose states associated with hepatic encephalopathy.
- in breast-feeding women
  Concerning use during pregnancy, see Section 4.6.

4.4 Special warnings and precautions for use

Urinary outflow must be secured. In patients with a partial obstruction of urinary outflow (e.g in patients with bladder-emptying disorders, prostatic hyperplasia or narrowing of the urethra), increased production of urine may provoke or aggravate complaints. Thus, these patients require careful monitoring - especially during the initial stages of treatment. Treatment with DESAL necessitates regular medical supervision. Particularly careful monitoring is necessary.

- İn patients with hypotension.

- İn patients who would be at particular risk from a pronounced fall in blood pressure, e.g. patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain.
- İn patients with latent or manifest diabetes mellitus.
- İn patients with gout.
- in patients with hepatorenal syndrome, i.e. functional renal failure associated with severe liver disease.
- in patients with hypoproteinaemia, e.g. associated with nephrotic syndrome (the effect of furosemide may be weakened and its ototoxicity potentiated). Cautious dose titration is required.
- in premature infants (possible development nephrocalcinosis/nephrolithiasis; renal function must be monitored and renal ultrasonography performed).

Regular 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 case of significant additional fluid loss (e.g. due to vomiting, diarrhoea or intense sweating). Hypovolaemia or dehydration as well as any significant electrolyte and acid-base disturbances must be corrected. This may require temporary discontinuation of furosemide.

Concomitant use with risperidone
In risperidone placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3%; mean age 89 years, range 75-97 years) when compared to patients treated with risperidone alone (3.1%; mean age 84 years, range 70-96 years) or furosemide alone (4.1%; mean age 80 years, range 67-90 years). Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.

No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination or co-treatment with other potent diuretics should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant treatment with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be avoided in elderly patients with dementia

<u>In the case of anaphylactic shock, the following initial steps are generally recommended:</u>

The injection is stopped immediately when the first symptoms such as sweating, nausea and cyanosis appear. The needle is left in the vena or an appropriate cannula is inserted to keep the vascular access open. Besides other usual measures, the patient is laid down with his head down and the airways kept open.

Medicines must be applied immediately:
i.v. epinephrine (adrenaline) is administered immediately:
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 slowly injected by checking the pulse and blood pressure (Attention should be paid to arrhythmias!). if necessary epinephrine injections can be repeated.
Then i.v. Glycocorticoids, for example 250-1000 mg methylprednisolone-21-hydrogen succinate are administered. If necessary, glucocorticoid doses are repeated (see package insert for these drugs).

Subsequently, volume substitution is performed intravenously using solutions such as plasma expander, Human-albumin, full electrolyte solution.

Other treatment steps:
administration of artificial breathing, oxygen inhalation, calcium and antihistamines. A pre-existing metabolic alkalosis (eg in decompensated liver cirrhosis) may worsen during furosemide treatment.
This medicinal product contains less than 1 mmol (23 mg) sodium in each ampoule, this mean it can be considered "sodium free".

4.5 Interactions with other medicinal products and other forms of interaction

FOOD
Whether and to what extent the absorption of furosemide is affected by taking it with food seems to depend on the pharmaceutical formulation. It is recommended that oral formulations of DESAL be taken on an empty stomach.

Not recommended associations:
In isolated cases intravenous administration of furosemide within 24 hours of taking chloral hydrate may lead to flushing, sweating attacks, restlessness, nausea, increase in blood pressure and tachycardia. Use of furosemide concomitantly with chloral hydrate is, therefore, not recommended.
Furosemide may potentiate the ototoxicity of aminoglycosides and other ototoxic drugs. Since this may lead to irreversible damage, these drugs must only be used 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, nephrotoxicity of cisplatin may be enhanced if furosemide is not given in low doses (e.g. 40 mg in patients with normal renal function) and with positive fluid balance when used to achieve forced diuresis during cisplatin treatment.

Oral furosemide and sucralfate must not be taken within 2 hours of each other because sucralfate decreases the absorption of furosemide from the intestine and so reduces its effect.

Furosemide decreases the excretion of lithium salts and may cause increased serum lithium levels, resulting in increased risk of lithium toxicity, including increased risk of cardiotoxic and neurotoxic effects of lithium. Therefore, it is recommended that lithium levels are carefully monitored in patients receiving this combination.

Patients who are receiving diuretics may suffer severe hypotension and deterioration in renal function, including cases of renal failure, 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 interrupting the administration of furosemide temporarily or at least reducing the dose of furosemide for three days before starting treatment with, or increasing the dose of, an ACE inhibitor or angiotensin II receptor antagonist.

Risperidone: Caution should be exercised and the risks and benefits of the combination or co-treatment with furosemide or with other potent diuretics should be considered prior to the decision to use. (See Section 4.4, regarding increased mortality in elderly patients with dementia concomitantly receiving risperidone).

Take into account:
Concomitant administration of non-steroidal anti-inflammatory drugs including acetylsalicylic acid may reduce the effect of furosemide. In patients with dehydration or hypovolaemia, non-steroidal anti-inflammatory drugs may cause acute renal failure. Salicylate toxicity may be increased by furosemide.

Attenuation of the effect of furosemide may occur following concurrent administration of phenytoin.

Corticosteroids, carbenoxolone, liquorice in large amounts, and prolonged use of laxatives may increase the risk of developing hypokalaemia.

Kortikosteroidler, karbenoksolon, büyük miktarlarda meyankökü ve uzayan laksatif kullanımı hipopotasemi gelişme riskini arttırabilir.

Some electrolyte disturbances (e.g. hypokalaemia, hypomagnesaemia) may increase the toxicity of certain other drugs (e.g. digitalis preparations and drugs inducing QT interval prolongation syndrome).

If antihypertensive agents, diuretics or other drugs with blood-pressure-lowering potential are given concomitantly with furosemide, a more pronounced fall in blood pressure must be anticipated.
Probenecid, methotrexate and other drugs which, like furosemide, undergo significant renal tubular secretion may reduce the effect of furosemide.
Conversely, furosemide may decrease renal elimination of these drugs. In case of high-dose treatment (in particular, of both furosemide and the other drugs), this may lead to increased serum levels and an increased risk of adverse effects due to furosemide or the concomitant medication.

The effects of antidiabetic drugs and blood-pressure-increasing sympathomimetics (e.g. epinephrine, norepinephrine) may be reduced. The effects of curare-type muscle relaxants or of theophylline may be increased.
The harmful effects of nephrotoxic drugs on the kidney may be increased.
Impairment of renal function may develop in patients receiving concurrent treatment with furosemide and high doses of certain cephalosporins.

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

Patients who were at high risk for radiocontrast nephropathy treated with furosemide experienced a higher incidence of deterioration in renal function after receiving radiocontrast compared to high-risk patients who received only intravenous hydration prior to receiving radiocontrast.

4.6 Pregnancy and lactation

Pregnancy category: C

Women with childbearing potential / Birth control (Contraception) There is insufficient data on the use of Furosemide in women with childbearing potential. Studies on animals have shown reproductive toxicity. The potential risk for humans is unknown.

LACTATION

Furosemide passes into breast milk and may inhibit lactation. Women must not breast-feed if they are treated with furosemide.

Reproductive ability / Fertility

Furosemide did not produced no impairment of fertility in male or female rats, at oral doses of 90 mg/kg/day and female mice at 200 mg / kg /day.

No significant embryotoxic or teratogenic effects were detected in various mammalian species such as mice, rats, cats, rabbits and dogs after treatment with furosemide. The furosemide (75 mg/kg/day) was given to pregnant rats on days 7-11 and 14-18 of the pregnancy. The delay in kidney maturation - reduction in the number of differential glomeruli - has been described.

Furosemide passes the placenta and reaches 100% of the maternal serum concentration in cord blood. No malformations in humans which might be associated with furosemide exposure have been reported to date. However, there is insufficient experience to allow a concluding evaluation of a potential damaging effect in the embryo/foetus. In utero urinary production can be stimulated in the foetus.

Following treatment of premature babies with furosemide, urolithiasis and nephrocalcinosis were observed.
No research research has been done to evaluate the effects of furosemide taken with breast milk on the baby.

4.7 Driving and using machines

Some adverse effects (e.g. an undesirably pronounced fall in blood pressure) may impair the patient's ability to concentrate and react, and, therefore, constitute a risk in situations where these abilities are of special importance (e.g. operating a vehicle or machinery).

4.8 ADVERSE REACTIONS

The frequencies are derived from literature data referring to studies where furosemide is used in a total of 1387 patients, at any dose and in any indication. When the frequency category for the same ADR was different, the highest frequency category was selected.

The following frequency rating is used, when applicable:
Very common ≥ 10 %; Common ≥ 1 and <10 % ; Uncommon ≥ 0.1 and < 1 %;
Rare ≥ 0.01 and < 0.1 %; Very rare < 0.01 %, Unknown (cannot be estimated from available data).

Blood and the lymphatic system disorders
Common : haemoconcentration
Uncommon : thrombocytopenia,
Rare : leucopoenia, eosinophilia
Very rare : agranulocytosis, aplastic anaemia or haemolytic anaemia

Immune system disorders
Rare : severe anaphylactic or anaphylactoid reactions (e.g. with shock)

Metabolism and nutrition disorders

Very common : electrolyte disturbances (including symptomatic), dehydration and hypovolaemia especially in elderly patients, blood creatinine increased, blood triglyceride increased
Common : hyponatremia, hypochloremia, hypokalaemia, blood cholesterol increased blood uric acid increased and attacks of gout,
Uncommon : glucose tolerance impaired. Latent diabetes mellitus may become manifest.
Not known : hypocalcemia, hypomagnesemia, blood urea increased , metabolic alkalosis, Pseudo-Bartter syndrome in the context of misuse and/or long-term use of furosemide.

Nervous system disorders
Rare : paraesthesiae
Common : hepatic encephalopathy in patients with hepatocellular insufficiency

Ear and labyrinth disorders
Uncommon : hearing disorders although usually transitory, particularly in patients with renal failure, hypoproteinaemia (e.g. in nephrotic syndrome) and/or when intravenous furosemide has been given too rapidly. Cases of deafness, sometimes irreversible have been reported after oral or IV administration of furosemide.
Rare : tinnitus.

Vascular disorders
Very common (for intravenous infusion) : Hypotension including orthostatic hypotension
Rare : vasculitis
Not known : thrombosis

Gastrointestinal disorders
Uncommon : nausea,
Rare : vomiting, diarrhoea
Very rare : pancreatitis acute

Hepato-biliary disorders
Very rare : cholestasis, transaminases increased

Skin and subcutaneous tissue disorders
Uncommon : pruritus, urticaria, rashes, dermatitis bullous, erythema multiforme, pemphigoid, dermatitis exfoliative, purpura, photosensitivity reaction
Not known : Stevens-Johnson syndrome, toxic epidermal necrolysis, AGEP (acute generalized exanthematous pustulosis) and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms)

Renal and urinary disorders

Common : urine volume increased

Rare : tubulointerstitial nephritis

Not known:

- urine sodium increased, urine chloride increase, urine retention (in patients with a partial obstruction of urinary outflow),
- nephrocalcinosis/nephrolithiasis in premature infants
- renal failure

Congenital and familial/genetic disorders

Not known : increased risk of persistence of patent ductus arteriosus when furosemide is administered to premature infants during the first weeks of life.

General disorders and administration site conditions

Not known : following intramuscular injection, local reactions such as pain

Rare : fever

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit / risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Turkey Pharmacovigilance Central at: (www.titck.gov.tr; e- post: tufam@titck.gov.tr; Tel: 0800 314 00 08; fax: O312 218 35 99).

4.9 Overdose and treatment

SIGNS AND SYMPTOMS

The clinical picture in acute or chronic overdose depends primarily on the extent and consequences of electrolyte and fluid loss, e.g. hypovolaemia, dehydration, haemoconcentration, cardiac arrhythmias (including A V block and ventricular fibrillation). Symptoms of these disturbances include severe hypotension (progressing to shock), acute renal failure, thrombosis, delirious states, flaccid paralysis, apathy and confusion.

MANAGEMENT:

No specific antidote to furosemide is known. If ingestion has only just taken place, attempts may be made to limit further systemic absorption of the active ingredient by measures such as gastric lavage or those designed to reduce absorption (e.g. activated charcoal).

Clinically relevant disturbances in electrolyte and fluid balance must be corrected. Together with the prevention and treatment of serious complications resulting from such disturbances and of other effects on the body, this corrective action may necessitate 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 handle diuretic that provides a relatively strong and short-acting fast-onset diuresis. Furosemide is a loop diuretic that inhibits the Na+/K+/2Cl- cotransporter in the ascending thick loop of Henle. therefore, the effectiveness of the saluretic effect of furosemide depends on the drug reaching the tubular lumen through an anion transport mechanism.

Furosemide promotes diuresis by blocking tubular reabsorption of sodium and chloride in loop of Henle. As a result, functional sodium excretion can reach 5 of glomerular sodium filtration.

Secondary effects of increased sodium excretion were 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, resulting in no attenuation of the saluretic activity. Furosemide causes dose-dependent stimulation of the renin -angiotensin -aldosterone system.

In case of heart failure, furosemide causes a acute reduction in the cardiatic preload (by dilation of the venous capitance vessels). This early vascular effect seems to be mediated by prostaglandins and requires an adequate renal function with the activation of the renin–angiotensin-aldosterone system and an intact prostaglandin synthesis. Apart from that, given its natriuretic effect, furosemide decreases vascular reactivity to catecholamines, which is increased in hypertensive patients.

The antihypertensive efficacy of furosemide is a consequence of the increased sodium excretion and a reduction of blood volume and a reduced responsiveness of vascular smooth muscle response to vasoconstrictor stimulation.

Pharmacodynamic properties:

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

A dose-dependent increase in diuresis and natriuresis was found in healthy individuals to whom furosemide was administerd (doses between 10 and 100 mg). The duration of action in healthy individuals after the administration of an intravenous 20 mg dose of furosemide is approximately 3 hours and 3 to 6 hours, when an oral 40 mg dose is given.

In ill patients, the relation between tubular concentration of free furosemide and bound furosemide (determined through the urine excretion rate) andits natriuretic effect is translated in a sigmoid graphic, with a minimum effective excretion rate of approximately 10 micrograms per minute. Consequently, a continuous infusion of furosemide is more effective than repeated bolus injections. Above a certain bolus administration dose, the drugs effects do not significantly increase. The efficacy of furosemide is decreased in cases of reduced tubular secretion or in cases of intra-tubular binding of the drug to albumin.

5.2 Pharmacokinetic properties

Absorption

Furosemide (frusemide) is rapidly absorbed from the GIT. The absorption of the drug varies widely among individuals. The bioavailability of furosemide in healthy volunteers is about 50% -70% for tablets and 80% for oral solution. In patients, the bioavailability of the drug is affected by various factors, including underlying diseases, and can be reduced by up to 30% (eg, in Nephrotic syndrome).
Whether absorption of furosemide is affected when taken with food depends on the pharmaceutical formulation.

Distribution

Furosemide distribution volume is 0.1 to 1.2 litres per kg of body weight. The distribution volume may be increased depending on the concomitant illness.

Furosemide is extensively bound to plasma proteins, mainly to albumin (higher than 98%).

Biotransformation: The glucuronic metabolite of furosemide represents 10% to 20% of the recovered substances in the urine.

Eliminasyon:
Furosemide is mostly eliminated as the non-conjugated form, mainly through secretion at the proximal tube. After intravenous administration, 60% to 70% of furosemide is eliminated by this manner. The remaining dose is eliminated in the faeces, probably after biliary secretion.

After intravenous administration, the plasma half-life of furosemide ranges from 1 to 1.5 hours. Furosemide is excreted in breast milk. It crosses the placental barrier transferring itself slowly to the foetus. Furosemide achieves similar concentrations in the mother, foetus and newborn.

Special Populations and Conditions

In renal/ hepatic impairment
In case of renal impairment, furosemide´s elimination is slower and its half-life is increased. In patients with severe renal failure the terminal half-life can reach 24 hours.

In case of nephrotic syndrome, the lower concentration of plasma proteins leads to higher concentrations of unbound furosemide . On the other hand, the efficiency of furosemide is reduced in these patients, due to intratubular albumin binding and to reduced tubular secretion.

Furosemide exhibits low dialysis in patients undergoing haemodialysis, peritoneal dialysis or CAPD (Chronic Ambulatory Peritoneal Dialysis).
In case of hepatic impairment, furosemide´s half-life increases 30% to 90%, mainly due to the higher distribution volume. In this group of patients, there is a wider variability of the pharmacokinetic parameters.

Congestive heart failure, severe hypertension, elderly:
The elimination of furosemide is delayed due to renal impairment in patients with congestive heart failure or severe hypertension as well as in the elderly
Premature infants and new-born:
Depending on the maturity of the kidney, elimination of furosemide may be slow. In case of children with insufficient capacity of glucuronidation, the metabolism of the drug is also reduced. In babies whose age is over 33 weeks after conception, the terminal half-life is under

12 hours. In infants of two months and older, terminal clearance is the same as in adults.

5.3 Preclinical safety data

Acute toxicity:
Studies with oral and intravenous administration to various rodents and dogs demonstrate low acute toxicity. Oral LD50 is 1,050-4,600 mg/kg in mice and rats and 243 mg/kg in guinea pigs. In dogs, oral LD50 is approximately 2,000 mg/kg and intravenous LD50> 400 mg/kg.

Chronic toxicity:
Studies in rats and dogs, who received 10-20 times the therapeutic dose for humans for 6 and 12 months, led to renal alterations (among others fibrous degeneration and renal calcification).

Ototoxicity:
Furosemide may affect the transport processes in the stria vascularis in the inner ear and may lead to a, usually reversible, hearing impairment.

Carcinogenicity:
Approximately 200 mg/kg (14,000 ppm) furosemide was given with the food to female mice and female rats for two years. Increased incidence of adenocarcinoma in mothers was seen in mice, but not in rats. The dose was significantly higher than the therapeutic doses in human patients. In addition, these tumors were morphologically identical to the spontaneously occurring tumors seen in 2-8% of control animals.
Thus, it seems unlikely that the increased tumor incidence is relevant to the treatment of humans. There is no evidence of increased incidence of human adenocarcinomas in mothers following furosemide treatment. A carcinogenic classification of furosemide in humans is not possible from available epidemiological studies.

In a carcinogenicity study furosemide was administered in doses of 15 and 30 mg/kg daily to rats. Male rats in the 15 mg/kg group, but not in the 30 mg/kg group, had a marginal increase in the occurrence of rare tumors. This finding is considered to be random.

Nitrosamine-induced urinary bladder carcinogenesis in rats did not indicate that furosemide is a promoter.

Mutagenicity:
Both positive and negative results were obtained in in vitro tests in bacteria and mammalian cells. However, induction of gene and chromosome mutations has been observed only when furosemide has reached cytotoxic concentrations.

Reproductive toxicity:
Fertility in both sexes of rats was not reduced at daily doses of 90 mg/kg or in mice of both sexes at daily oral doses of 200 mg/kg.

No relevant embryo toxic or teratogenic effects were observed in a variety of mammalian species, including mice, rats, cats, rabbits and dogs after treatment with furosemide. Delayed renal impairment (decreased number of differentiated glomeruli) has been reported in rat offspring following administration of 75 mg/kg during day 7-11 and day 14-18 of gestation.

Furosemide crosses the placental barrier, and the concentration of furosemide in the umbilical cord blood is the same as the mother’s serum concentration. No malformations in humans

which might be associated with exposure to furosemide have been reported to date. However, there is limited experience to allow a conclusive evaluation of a potential harmful effect in the fetus. Fetal urine production can be stimulated in the uterus.

Urolithiasis and nephrocalcinosis have been observed in premature babies after maternal treatment with furosemide.
No studies have been conducted to assess whether infants are affected by furosemide secreted in breast milk.

6. Pharmaceutical particulars

6.1 List of excipients
Sodium Chloride.
Sodium Hydroxide.
Water for Injections.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
60 Months

6.4 Special precautions for storage
Store below 25° C and protect from light.

6.5 Nature and contents of container
DESAL ampoules are available in packages containing 5 and 100 ampoules of 2 ml (= 20 mg).

6.6 Special precautions for disposal and other handling
Unused products or waste materials should be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging Waste Control Regulation".

7. Marketing authorisation holder

STOT PHARMA İlaç Sanayi ve Dış Tic. Ltd. Şti.
Emek Mah. 29. Sk. No:4 A Antakya-Hatay

8. Marketing authorisation number(s)

2019/382

9. Date of first authorisation date /renewal of the authorisation

First authorisation date: 08.08.2019

10. Date of revision of the text