

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Furosemide 500 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg furosemide.

Excipient(s) with known effect:

Each tablet contains 111.8 mg lactose monohydrate equivalent to 106.2 mg lactose.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Light yellow, round flat tablets of 13 mm diameter, with bevelled edges, debossed “FUS” on one side and quartering score lines on the other.

The tablet can be divided into equal doses or quarters.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Furosemide 500 mg tablets are destined for use exclusively in patients with severely reduced glomerular filtration (glomerular filtration rate (GFR) < 20 ml/min).

Furosemide 500 mg Tablets are indicated as a diuretic in the management of oliguria in chronic renal insufficiency (see section 4.4).

4.2 Posology and method of administration

Posology

For oral administration

The dosage should be adjusted individually, predominantly on the basis of response to treatment. The lowest effective dose should be always used.

Adults

The initial dose is 250 mg furosemide (half a tablet).

The dose should be carefully adjusted in patients with chronic renal insufficiency in order to gradually resolve oedema: if a satisfactory diuresis is not achieved the dose may be increased in steps of 250 mg at 4-6 hourly intervals up to a maximum dose of 2 tablets (1,000 mg).

The patient's hydration status and serum electrolytes should be monitored and the response to treatment periodically evaluated.

The duration of treatment depends on the nature and severity of the disease.

Paediatric population

The 500 mg strength is not recommended for use in children and adolescents under 18 years of age due to insufficient data on safety and efficacy: other pharmaceutical forms/strengths may be more appropriate for administration to this population.

Patients with Hepatic impairment

Cautious titration is recommended until the required response is achieved (see also sections 4.3 and 4.4).

Elderly

Cautious titration is recommended until the required response is achieved.

Method of administration

For oral administration: the tablet should be swallowed whole, unchewed, without food and with a sufficient amount of fluid (*e.g.* a glass of water).

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
- Normal renal clearance and reduced renal function with GFR > 20 ml/min, owing to the risk of severe fluid and electrolyte loss in such cases,
- Renal failure with anuria,
- Hepatic coma and pre-coma,
- Hypokalaemia,
- Hyponatraemia,
- Hypovolaemia or dehydration,
- Lactation,
- Cardiac glycoside intoxication.

4.4 Special warnings and precautions for use

The diuretic effect should be monitored by periodic dechallenge of the diuretic agent.

Particularly careful monitoring is required in patients with:

- Hypotension,
- Manifest or latent diabetes mellitus (blood glucose should be monitored regularly),
- Gout (serum uric acid should be monitored regularly),
- Urinary tract obstruction (*e.g.* prostate hypertrophy, hydronephrosis, ureteral stenosis),
- Hypoproteinaemia, *e.g.* in nephrotic syndrome (the dose should be carefully titrated),
- Hepatic cirrhosis and concomitant renal impairment,
- Patients at particular risk from a sudden, unexpected drop in blood pressure, *e.g.* patients with cerebrovascular disorders or coronary heart disease,

- Premature infants (risk of nephrocalcinosis/nephrolithiasis; the renal function should be monitored and renal sonography carried out).

In premature children with respiratory distress syndrome, diuretic treatment with furosemide in the first weeks of life may increase the risk of a patent *ductus arteriosus*.

Symptomatic hypotension leading to dizziness, fainting or loss of consciousness can occur in patients treated with furosemide, particularly in the elderly, patients on other medications which can cause hypotension and patients with other medical conditions that are risks for hypotension.

Furosemide should only be given to patients with micturition disorders (*e.g.* prostate hypertrophy) when care is taken to maintain an unobstructed flow of urine, as a sudden flux of urine could lead to anuria with over-extension of the bladder.

Serum electrolytes (especially potassium, sodium, calcium), bicarbonate, creatinine, urea, uric acid and blood glucose should be regularly monitored during long-term therapy with furosemide. Particularly close monitoring is necessary in patients at high risk of electrolyte disorders or in the event of significant fluid loss (*e.g.* owing to acute hypercalcaemia, vomiting, diarrhoea or intense sweating). The risk of hypokalaemia must be especially taken into consideration in the presence of hepatic cirrhosis, concurrent corticosteroid therapy or laxative abuse, limited diet). Furosemide may also exacerbate pre-existing metabolic alkalosis. Consequently, hypovolaemia, dehydration, electrolyte disorders and acid-base imbalances must be corrected. This may require temporary discontinuation of furosemide treatment.

The weight loss resulting from increased urine excretion should not exceed 1 kg/day independently from the degree of urine excretion.

The dose should be adjusted with caution in patients with nephrotic syndrome owing to the increased risk of adverse events.

Concomitant administration with risperidone

A higher incidence of mortality was observed in placebo-controlled studies in elderly patients with dementia in individuals treated with furosemide and risperidone (7.3%, average age 89 years, range 75-97 years) compared to those on risperidone alone (3.1%, average age 84 years, range 70-96 years) or furosemide alone (4.1%, average age 80 years, range 67-90 years). The concomitant administration of risperidone with other diuretics (mostly low-dose thiazides) was not associated with a similar finding.

No pathophysiological mechanism and no single causal pattern for the deaths emerged from these observations. Consequently, caution is required, and the risks and indication of this combination or the association of other potent diuretics with risperidone should be weighed before initiating treatment. The incidence of mortality was not increased in patients treated with other diuretics in combination with risperidone. Independently from treatment, dehydration was a general risk factor for mortality and should therefore be avoided in elderly patients with dementia (see section 4.3).

Furosemide is not recommended for preventative diuresis in patients at high risk for radiocontrast nephropathy (see section 4.5).

The administration of furosemide 500 mg may lead to positive results in anti-doping tests. Furthermore, the use of furosemide as a doping substance may endanger health.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant administration of furosemide and glucocorticoids, carbenoxolone or laxatives may lead to increased potassium loss with the risk of hypokalaemia. Large quantities of liquorice act like carbenoxolone in this respect.

Concomitant administration of carbamazepine may increase the risk of hyponatraemia.

Non-steroidal anti-inflammatory agents (NSAIDs) (*e.g.* indomethacin, acetylsalicylic acid) may reduce the effect of furosemide. NSAIDs may lead to acute renal failure in patients on furosemide who develop hypovolaemia or dehydration.

Probenecid, methotrexate and other agents which undergo significant renal tubular secretion like furosemide may reduce its effect. Furosemide may reduce the renal elimination of such substances which may result in increased serum levels and a higher risk of adverse events, especially in patients on high-dose therapy of either furosemide or the associated agent.

The concomitant administration of phenytoin has been reported to reduce the effect of furosemide.

As sucralfate reduces the intestinal uptake of furosemide and therefore reduces its effect, the two substances should be administered at least 2 hours apart.

Account should be taken of the fact that myocardial sensitivity to cardiac glycosides may be increased owing to furosemide-induced hypokalaemia and/or hypomagnesaemia. The risk of ventricular arrhythmias (including *torsades de pointes*) may be increased in combination with agents associated with long QT syndrome (*e.g.* terfenadine, some class I and III anti-arrhythmic agents) and in the presence of electrolyte disorders.

The toxicity of high-dose salicylates may be increased during concomitant treatment with furosemide.

Furosemide may increase the adverse effects of nephrotoxic agents (*e.g.* antibiotics such as aminoglycosides, cephalosporins, polymyxins).

Deterioration of renal function may occur in patients receiving furosemide with high doses of some cephalosporins.

The ototoxicity of aminoglycosides (*e.g.* kanamycin, gentamicin, tobramycin) and other ototoxic agents may be increased when they are used concomitantly with furosemide. The resulting hearing disturbances may be irreversible. The association of these agents should therefore be avoided.

The possibility of hearing disorders should be taken into account when administering cisplatin and furosemide together. If forced diuresis with furosemide is considered necessary during treatment with cisplatin, furosemide should only be used in low doses (*e.g.* 40 mg for normal renal function) and with in patients with a positive fluid balance. Otherwise, the nephrotoxicity of cisplatin may be increased.

The combination of furosemide and lithium leads to reduced lithium excretion and consequently to an increase in the cardio- and neurotoxic effects of lithium. Lithium levels should therefore be carefully monitored in patients requiring such combined treatment.

A marked fall in blood pressure should be expected on concomitant administration of furosemide with other antihypertensives, diuretics or agents with the potential to decrease the blood pressure. In particular, massive reductions in blood pressure to the point of shock and worsening of renal function (in isolated cases acute renal failure) have been reported when angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB) were administered for the first time, or for the first time at a higher dose. Where possible, furosemide should therefore be temporarily discontinued or at least the dose reduced for 3 days prior to the initiation or up-titration of ACE inhibitor or ARB treatment.

Furosemide may increase the effect of theophylline and curare-type muscle relaxants.

Furosemide may reduce the effect of anti-diabetic agents and pressor amines (*e.g.* epinephrine, norepinephrine).

Caution is recommended in patients on risperidone, and the risks and indication of concomitant administration with furosemide or other potent diuretics should be weighed prior to initiation (see section 4.4).

The concomitant administration of ciclosporin A and furosemide has been linked to an increased risk of gout, as a result of furosemide-induced hyperuricaemia and the influence of ciclosporin on renal uric acid excretion.

Worsening renal function was more common after contrast radiological examination in patients at high risk of contrast media-associated disorders treated with furosemide than in those who received only intravenous hydration prior to the procedure.

In isolated cases, hot flushes, perspiration, unrest, nausea, increases in blood pressure and tachycardia have been observed within 24 hours after the administration of chloral hydrate and intravenous furosemide. The concomitant use of furosemide and chloral hydrate should therefore be avoided.

4.6 Fertility, pregnancy and lactation

Pregnancy

Furosemide should only be used during pregnancy for short periods if absolutely necessary, as it crosses the placenta.

Diuretics are not routinely indicated for the treatment of hypertension and oedema in pregnancy since they reduce placental perfusion and consequently intra-uterine growth.

If furosemide is required to treat cardiac or renal insufficiency in pregnancy, electrolyte and haematocrit levels and fetal growth must be monitored closely. Displacement of bilirubin from albumin binding and a resulting increase in the risk of nuclear jaundice in hyperbilirubinaemia have been reported with furosemide.

Furosemide crosses the placenta and reaches 100% of maternal serum concentrations in umbilical blood. No malformations have been reported in humans to date which could be linked to exposure to furosemide. There are insufficient data to definitively determine its potential harmful effects on the embryo/fetus. Fetal urine production *in utero* may be stimulated. Urolithiasis has been reported in premature infants treated with furosemide.

Breast-feeding

Furosemide is excreted in breast milk and inhibits lactation. Furosemide should therefore not be given to breast-feeding women. Otherwise, breast-feeding should be discontinued (see section 4.3).

4.7 Effects on ability to drive and use machines

Furosemide has minor influence on the ability to drive and use machines. It may elicit diverse individual reactions which might impair the ability to drive and use machines, especially at the beginning therapy, on increasing the dose or changing the treatment and in association with alcohol.

4.8 Undesirable effects

Adverse events are categorized by frequency as follows:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1,000 to <1/100
Rare	≥1/10,000 to <1/1,000
Very rare	<1/10,000
Not known	(cannot be estimated from the available data)

Blood and lymphatic system disorders:

<i>Uncommon:</i>	Thrombocytopenia
<i>Rare:</i>	Eosinophilia, leucopenia
<i>Very rare:</i>	Haemolytic anaemia, aplastic anaemia, agranulocytopenia

Immune system disorders:

<i>Uncommon:</i>	Pruritus, skin and mucous membrane reactions (see skin and subcutaneous disorders)
<i>Rare:</i>	Fever, vasculitis, interstitial nephritis, severe anaphylactic and anaphylactoid reactions such as anaphylactic shock (see section 4.9)

Endocrine disorders:

The glucose tolerance may deteriorate with furosemide and hyperglycaemia may develop. In patients with manifest diabetes mellitus this may lead to worsening of the metabolic situation. Latent diabetes mellitus may become overt.

Metabolism and nutrition disorders:

<i>Common:</i>	Fluid and electrolyte disorders are frequently observed during treatment with furosemide owing to the increased electrolyte excretion. Regular monitoring of serum electrolytes (in particular potassium, sodium and calcium) is therefore recommended.
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The possibility of electrolyte disorders depends on co-morbidities (*e.g.* hepatic cirrhosis, cardiac insufficiency), concomitant therapy (see section 4.5) and nutrition.

Hyponatraemia and corresponding symptoms may result from increased renal sodium loss, in particular in the presence of reduced sodium intake. The commonest symptoms of sodium depletion are apathy, leg cramps, loss of appetite, vomiting and confusion.

Hypokalaemia, which may be associated with neuromuscular (muscle weakness, paraesthesia, paresis), intestinal (vomiting, constipation, tympanites), renal (polyuria, polydipsia) and cardiac (pacemaker and conduction disorders) symptoms, may result from increased renal potassium loss, especially with concomitant reduced potassium intake and/or increased extra-renal potassium loss (*e.g.* with vomiting or chronic diarrhoea). Severe potassium loss may lead to paralytic ileus or loss of consciousness and coma.

Increased calcium loss may lead to hypocalcaemia. In rare cases this may result in tetany.

Increased renal magnesium loss may lead to hypomagnesaemia and, in rare cases, result in tetany or cardiac rhythm disorders.

Metabolic alkalosis may develop or worsen as a consequence of electrolyte and fluid loss during treatment with furosemide.

Hyperuricaemia commonly develops during treatment with furosemide, which may lead to gout in predisposed patients.

Serum cholesterol and triglyceride levels may increase during treatment with furosemide.

Nervous system disorders:

Rare: Paraesthesia

Not known: Dizziness, fainting and loss of consciousness (caused by symptomatic hypotension)

Hepatic encephalopathy may occur in patients with hepatic insufficiency.

Ear and labyrinth disorders:

Rare: Mostly reversible hearing disorders and/or tinnitus may rarely occur due to the ototoxicity of furosemide. This possibility should be taken into account especially for rapid intravenous injection, in particular in patients with renal insufficiency or hypoproteinaemia (e.g. in nephrotic syndrome).

Uncommon: Deafness (sometimes irreversible)

Vascular disorders:

Excessive diuresis may lead to circulatory disorders, especially in the elderly and children, which manifest primarily as headache, dizziness, visual disturbances, mouth dryness and thirst, hypotension and orthostatic regulation disorders. Dehydration, circulatory collapse due to hypovolaemia and haemoconcentration may occur. The latter may increase the risk of thrombosis, particularly in the elderly.

Gastrointestinal disorders:

Rare: Gastrointestinal disorders (e.g. nausea, vomiting, diarrhoea)

Hepatobiliary disorders:

Very rare: Acute pancreatitis, intra-hepatic cholestasis, increased hepatic transaminase levels

Skin and subcutaneous tissue disorders:

Uncommon: Pruritus, skin and mucous membrane reactions (e.g. bullous exanthema, urticaria, purpura, erythema multiforme, bullous pemphigoid, exfoliative dermatitis, photosensitivity)

Rare: Vasculitis

Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis

Not known: acute generalised exanthematous pustulosis (AGEP)

Renal and urinary disorders:

Transient increases in serum creatinine and urea levels may be observed. Symptoms of urinary tract obstructions (e.g. in prostate hyperplasia, hydronephrosis, ureteral stenosis) may develop or worsen with furosemide. Urine retention with secondary complication may occur.

Rare: Interstitial nephritis

Pregnancy, puerperium and perinatal conditions:

Nephrolithiasis and/or nephrocalcinosis may occur in premature infants treated with furosemide.

In premature children with respiratory distress syndrome, diuretic treatment with furosemide in the first weeks of life may increase the risk of a patent *ductus arteriosus*.

General disorders and administration site conditions:

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms

The clinical picture of acute or chronic overdose depends on the degree of fluid and electrolyte loss. Overdose may lead to hypotension, orthostatic regulation disorders, electrolyte disorders (hypokalaemia, hyponatraemia, hypochloraemia) or alkalosis. Severe fluid loss may result in marked hypovolaemia, dehydration, circulatory collapse and haemoconcentration with risk of thrombosis. Delirium may occur with rapid fluid and electrolyte loss. Anaphylactic shock (symptoms: perspiration, nausea, cyanosis, severe hypotension, loss of consciousness, coma) may rarely develop.

Treatment

Furosemide must be immediately discontinued in the event of overdose or on development of signs of hypovolaemia (hypotension, orthostatic regulation disorders).

Primary poison management measures (induced vomiting, gastric lavage) and measures to reduce absorption (medicinal charcoal) should be taken if the overdose is recent.

In severe cases, vital signs must be monitored and the fluid, electrolyte and acid-base balance, blood glucose and renally excreted substances repeatedly evaluated, and any necessary corrective measures taken.

In patients with micturition disorders (*e.g.* prostate hypertrophy), an unobstructed flow of urine must be maintained, as a sudden flux of urine could lead to anuria with over-extension of the bladder

Treatment of hypovolaemia: volume expansion

Treatment of hypokalaemia: potassium substitution

Treatment of circulatory collapse: shock position, if necessary, shock therapy

Immediate treatment measures in the event of anaphylactic shock: at the first signs (*e.g.* cutaneous reactions such as urticaria, flush, unrest, headache, perspiration, nausea, cyanosis)

- maintain circulation
- maintain patent airway, administer oxygen
- further measures, including intensive care measures, may be required (including administration of epinephrine, volume substitution, glucocorticoids).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: high-ceiling diuretics; sulphonamides, plain
ATC code: C03C A01

Mechanism of action:

Furosemide is a potent, short- and rapid-acting loop diuretic. It inhibits sodium, chloride and potassium re-absorption in the ascending limb of the loop of Henle by blocking the $\text{Na}^+/2\text{Cl}^-/\text{K}^+$ transporter. Fractional sodium excretion may thus reach 35% of glomerular sodium filtration. As a result of the increased sodium excretion, urine secretion and distal tubular potassium secretion are augmented secondary to osmotic water movement. Calcium and magnesium excretion are similarly

increased. Uric acid excretion may be reduced and the acid-base balance disrupted towards metabolic alkalosis in parallel with these electrolyte losses.

Pharmacodynamic effects:

Furosemide interrupts the tubulo-glomerular feedback mechanism to the macula densa, so the saluretic effect is not reduced.

Furosemide causes dose-dependent stimulation of the renin-angiotensin-aldosterone system.

In heart failure, furosemide acutely reduces the cardiac preload by dilating venous capacity vessels. This early vascular effect seems to be mediated by prostaglandins and presupposes and sufficient renal function with activation of the renin-angiotensin-aldosterone system and intact prostaglandin synthesis.

Furosemide reduces blood pressure by increasing sodium excretion and reducing the reactivity of vascular smooth muscle to vasoconstrictive stimulation as well as by reducing blood volume.

5.2 Pharmacokinetic properties

Absorption:

After oral administration, 60-70% of furosemide is absorbed from the gastrointestinal tract. This may be reduced to less than 30% in patients with chronic heart failure or nephrotic syndrome.

The onset of the effect of furosemide occurs after approximately 30 minutes. Peak plasma concentrations occur within approximately an hour after ingestion of a tablet.

Distribution:

The plasma protein binding of furosemide is approximately 95%. This may be reduced to 10% in renal insufficiency. The relative volume of distribution is approximately 0.2 l/kg body weight (0.8 l/kg body weight in neonates).

Biotransformation:

Furosemide is only slightly metabolised in the liver (approximately 10%) and is mostly excreted unchanged.

Elimination:

Its elimination is two thirds renal, and one third biliary/faecal. The elimination half-life is approximately 1 hour with normal renal function; it may be increased up to 24 hours in terminal renal insufficiency.

Special populations

Paediatric population

Depending on the maturity of the kidney, the elimination of furosemide may be slowed down. Its metabolism is also reduced if the infant's glucuronisation capacity is impaired. The terminal half-life is below 12 hours in infants with a post-conceptual age of more than 33 weeks. In infants of 2 months and older, the terminal clearance is the same as in adults.

Elderly

The elimination of furosemide is slowed down due to reduced renal function in the elderly.

Hepatic impairment

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

Renal impairment

In renal failure, the elimination of furosemide is slowed down and the half-life prolonged; the terminal half-life may be up to 24 hours in patients with severe renal failure. In the nephrotic syndrome the reduced plasma protein concentration leads to a higher concentration of unbound (free) furosemide. On the other hand, the efficacy of furosemide is reduced in these patients due to binding to intratubular albumin and lowered tubular secretion.

Furosemide is poorly dialysable in patients undergoing haemodialysis, peritoneal dialysis and continuous ambulatory peritoneal dialysis.

5.3 Preclinical safety data

The acute oral toxicity was low in all tested species. Chronic toxicity studies in rats and dogs indicated changes in the kidneys (including renal fibrosis and calcification).

In vitro and *in vivo* evaluations of genetic toxicology did not reveal any clinically relevant indications of genotoxic potential.

Long-term studies in rats and mice did not indicate any carcinogenic potential.

Reproduction toxicity studies with high doses revealed a reduced number of differentiated glomeruli, skeletal abnormalities in the scapula, humerus and ribs due to hypokalaemia in rat fetuses, and hydronephrosis in mouse and rabbit fetuses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Silica, colloidal anhydrous
Talc
Magnesium stearate
Iron oxide, yellow (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Blister (white opaque PVC/PVdC – Aluminium blisters)

Pack sizes: 20, 28, 30, 50, 60, 90 & 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

TEVA UK Limited
Brampton Road,
Hampden Park,
Eastbourne,
East Sussex BN22 9AG
UNITED KINGDOM

8. MARKETING AUTHORISATION NUMBER(S)

PL 00289/1420

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/12/2010

10. DATE OF REVISION OF THE TEXT

05/02/2016