Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Furosemide Clonmel 20 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Furosemide Clonmel 20 mg tablet contains 20 mg of furosemide.

Excipient(s) with known effect
Each Furosemide Clonmel 20 mg tablet contains 49.9 mg lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Furosemide Clonmel 20 mg tablet is white to off white, round tablet, 6 mm in diameter, marked with F and 20 on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of oedema associated with

- cardiac disease
- liver disease (most often in combination with a potassium-sparing diuretic)
- renal disease, including nephrotic syndrome. In patients with nephrotic syndrome, therapy of the underlying disorder has priority.

Treatment of arterial hypertension.

4.2 Posology and method of administration

Posology

The dose should be determined individually.

Treatment of oedema due to cardiac, liver or renal disease

Adults
The initial adult dose is 20-40 mg daily. The dose should be adjusted until the lowest effective dose is achieved as a maintenance dose. In some patients, daily maintenance doses of 80 mg or higher (given in divided doses) may be required.
If initial dose (40 mg) does not provide sufficient diuresis, the patient may be given the dose 80 mg after 6 hours from the initial dose have elapsed. If diuresis is still not sufficient, the patient may be given the dose 160 mg after 6 hours from the previous dose have elapsed.
If necessary and under strict clinical supervision, exceptionally also doses of furosemide exceeding 200 mg may be used. The weight loss caused by increased urinary excretion should not exceed 1 kg/day (see section 4.4).
The maximum daily dose of furosemide administration is 1500 mg.

Paediatric population
The recommended dose range is 1-2 mg/kg bodyweight per day (given in one or divided doses), however total daily dose should not exceed 40 mg.

For children not able to swallow the tablets other more suitable pharmaceutical forms containing furosemide may be on the market.

Arterial 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 (in case of contraindication to diuretics thiazides (especially when creatinine clearance is less than 30 ml/min)) usually the recommended dose is 20 mg to 120 mg of furosemide per day in one dose or divided in doses, alone or in combination with other antihypertensive medicinal products (most commonly angiotensin II receptor blockers (ARBs)).

Elderly
Caution is advised as furosemide is eliminated more slowly in elderly patients. Treatment should be titrated upwards as required (see section 4.4).

Renal impairment
In case of renal insufficiency, less furosemide will reach the renal tubules. An increase of dose may be necessary to obtain the same diuretic effect.
In the case of nephrotic syndrome the effect of furosemide may be weakened and its ototoxicity potentiated; therefore cautious dose titration is required.

Hepatic impairment
No dose adjustment is needed for patients with mild hepatic impairment. However, the dose may require adjustment in cases of moderate to severe hepatic impairment.

Clinical monitoring requirements
Serum potassium should be closely monitored after treatment initiation and in subjects with concomitant treatment with cardiac glycosides, such as digoxin (see section 4.4 also for other recommended monitoring).

Treatment duration should be determined according to the indication and severity of disease.

Method of administration
For oral administration.

Tablets should be taken on an empty stomach. Tablets should not be chewed.

4.3 Contraindications

Furosemide is contraindicated in the following circumstances:

- hypersensitivity to the active substance, sulfonamides or to any of the excipients listed in section 6.1

Patients allergic to sulfonamides (e.g. sulfonamide antibiotics or sulfonylureas) may show cross-sensitivity to furosemide.

- renal failure with anuria
- hypovolaemia or dehydration (with or without accompanying hypotension) (see section 4.4)
- severe hypokalaemia, severe hyponatraemia (see also section 4.4)
- breast-feeding women (see section 4.6)
- pre-coma/coma associated with hepatic cirrhosis or encephalopathy (see also section 4.4)
- evolving hepatitis and severe hepatocellular insufficiency in haemodialysis patients and patients with severe renal insufficiency (creatinine clearance < 30 ml/min), due to the risk of furosemide accumulation, since its elimination is mainly via the biliary route (see section 4.4)
- obstruction in the urinary tract (see also section 4.4).

4.4 Special warnings and precautions for use

Particularly careful monitoring is necessary in case of:

- hypotension
- patients who are at special risk from a pronounced fall in blood pressure, e.g., patients with cerebrovascular perfusion disorders or coronary heart disease (see also below)
- latent or manifest diabetes (regular monitoring of blood glucose values is recommended)
- hepatorenal syndrome (rapidly progressive renal insufficiency associated with severe liver disease, e.g., liver cirrhosis)
- hepatocellular insufficiency, due to risk of development of hepatic encephalopathy (regular monitoring of serum electrolytes is recommended). If this occurs treatment with furosemide should be discontinued immediately (see section 4.3).
- hypoproteinaemia, in particular in the case of nephrotic syndrome (the effect of furosemide may be weakened and its ototoxicity potentiated) (see section 4.2).
- gout, since furosemide may lead to hypovolaemia/hyponatremia which reduces excretion of uric acid with urine and leads to hyperuricaemia which makes the patient more prone to attacks of gout (regular monitoring of serum uric acid values is recommended)
- concomitant use with lithium (careful monitoring of lithium plasma levels and modification of lithium dosage is recommended) (see section 4.5)
- premature infants (see below)

Hypotension and/or hypovolaemia
Symptomatic hypotension leading to dizziness, vertigo or loss of consciousness can occur in some patients treated with furosemide, especially in elderly patients, patients taking other medications that may cause hypotension and in patients with other medical conditions that present risk for hypotension (see section 4.3).

Obstruction of urinary outflow and impaired micturition
Urinary output must be ensured. Patients with partial obstruction of urinary outflow (e.g. patients with impaired micturition, hydronephrosis and urethral stricture), have an increased risk of developing acute retention and careful monitoring - especially during the initiation of treatment – is required.
Furosemide may be used in patients with impaired micturition (e.g., in prostatic hyperplasia) only if diuresis is not impaired, as sudden polyuria may lead to ischuria with overextension of the bladder. See also section 4.3.

Electrolyte disorders
Impairment of electrolyte and fluid balance as a consequence of increased electrolyte excretion are commonly observed during therapy with furosemide. Regular monitoring of serum electrolytes (especially potassium, sodium and calcium) is therefore indicated. During long-term therapy with furosemide, regular monitoring of hydrogencarbonate, creatinine, urea and uric acid, as well as blood glucose is also recommended.

An especially close monitoring is necessary in patients with a high risk of developing electrolyte disorders in case of higher fluid losses (e.g., due to emesis, diarrhoea or intense diaphoresis), or due to underlying disorders (e.g. hepatocirrhosis, heart failure), concomitant medication (see section 4.5) and nutrition. Hypovolaemia or dehydration as well as considerable electrolyte disorders or disorders in the acid-base balance must be corrected. This may require treatment to be discontinued temporarily.

Hypokalaemia
The risk of hypokalaemia should be considered, especially in the beginning of the treatment and in patients concomitantly treated with digitalis (see sections 4.2, 4.5, 4.8 and 4.9).
Potassium depletion with hypokalaemia constitutes a major risk when using loop diuretics. The risk of developing hypokalaemia (< 3.5 mmol/L) should be avoided in certain at-risk populations such as the elderly and/or malnourished and/or taking multiple medications, cirrhotic patients with oedema and ascites, coronary artery disease, and heart failure.
Hypokalaemia increases the cardiac toxicity of digitalis and the risk of rhythm disturbances. In patients with a long QT interval on the ECG, whether congenital or drug-induced, hypokalaemia promotes the occurrence of severe rhythm disturbances, particularly *torsades de pointes*, which can be fatal, especially in the presence of bradycardia. In all cases, more frequent monitoring of serum potassium is necessary. The first plasma potassium monitoring should be performed within one week of starting treatment.

As furosemide can lead to hypokalaemia, a potassium rich diet is always indicated (e.g. potatoes, bananas, tomatoes, spinach, dry fruits etc.).
If necessary treatment of patients with potassium supplements or potassium sparing diuretics may be considered.

Hyponatraemia
Serum sodium levels should be monitored before starting treatment and at regular intervals thereafter. Any diuretic treatment can cause hyponatraemia, which can have serious consequences (see section 4.3)
As decrease in serum sodium levels may initially be asymptomatic, regular monitoring is therefore essential and should be even more frequent in at-risk populations such as the elderly, especially those who are malnourished, and cirrhotic patients (see sections 4.5, 4.8 and 4.9).

Supplements
During long term treatment with furosemide, thiamine should be supplemented. Thiamine deficiency due to increased renal excretion can contribute to a reduction in myocardial contractility.

Weight loss
The weight loss caused by increased urinary excretion should not exceed 1 kg/day, irrespective of the extent of urinary excretion.

Systemic lupus erythematosus
The possibility exists of exacerbation or activation of systemic lupus erythematosus hence caution should be taken when administering furosemide to patients with a history of SLE.

Photosensitivity
Photosensitivity reactions have been reported in patients taking furosemide (see section 4.8). If photosensitivity reaction occurs it is recommended to stop the treatment with furosemide. If re-administration of the treatment is essential, it is recommended to protect exposed areas from sunlight or artificial UVA.

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 (see sections 4.3 and 4.5).

Paediatric population
Premature infants
Risk of development of nephrocalcinosis/ nephrolithiasis; renal function must be monitored, and renal ultrasonography performed.
In premature infants with respiratory distress syndrome, diuretic treatment with furosemide during the first weeks of life can increase the risk of persistent ductus arteriosus Botalli.

Excipients
Lactose: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
Sodium: This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Contaminant use is not recommended

Chloral hydrate

In isolated cases, heat sensation, increased sweating, agitation, nausea, rise in blood pressure and tachycardia may occur after intravenous administration of furosemide within 24 hours after intake of chloral hydrate. Concomitant administration of furosemide and chloral hydrate is therefore to be avoided.

Medicinal products causing ototoxicity

The ototoxicity of glycopeptides (e.g., vancomycin and teicoplanin), aminoglycosides (e.g., kanamycin, gentamicin, tobramycin), organoplatins (platinum compounds) and loop diuretics may be increased in concurrent administration of furosemide. Dysacusis can be irreversible. Concomitant use of the above-named medicinal products should therefore be avoided. If such a combination is necessary, hearing function should be monitored closely.

Combinations to be used with precaution

Cisplatin

If furosemide is used concomitantly with cisplatin (a platinum compound), the possibility of auditory damage is to be expected. If forced diuresis with furosemide is aimed at during cisplatin treatment, furosemide may be administered only at low dose (e.g., 40 mg in normal renal function) and in positive fluid balance. Otherwise, increased nephrotoxicity of cisplatin may occur.

Sucralfate

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.

Lithium

Co-administration of furosemide and lithium leads to an increase in the cardiotoxic and neurotoxic effects of lithium via reduced lithium excretion. If the combination cannot be avoided, it is therefore recommended to carefully monitor the lithium plasma level of patients receiving this combination (see section 4.4).

Medicinal products causing hypotension

If antihypertensive agents, diuretics or other active substances with blood-pressure-lowering potential are given concomitantly with furosemide, a more pronounced fall in blood pressure must be anticipated. Monitor blood pressure and adjust the dose of the antihypertensive agent if necessary.

ACE inhibitors, ARBs

Massive reduction in blood pressure to the point of shock in extreme cases and worsening of renal function (acute renal failure in isolated cases) 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 high dose. If possible, furosemide therapy should be temporarily discontinued or the furosemide dose should be reduced for three days before therapy with an ACE inhibitor or angiotensin II receptor blockers (ARB) is initiated or the dose of an ACE inhibitor or angiotensin II receptor blockers (ARB) is increased.
In congestive heart failure treated with diuretics, start with a very low dose of ACE inhibitor, possibly after reducing the dose of the associated hypokalaemic diuretic.
In all cases, monitor renal function (serum creatinine measurement) during the first weeks of treatment with an ACE inhibitor or an angiotensin II receptor blocker (ARB).

Other medicinal products causing hypotension

Concomitant use of furosemide with the following medicinal products increases the risk of hypotension, particularly orthostatic hypotension:

- Imipramine antidepressants
- Neuroleptics
- Amifostine
- Alpha-blockers for urological use: alfuzosin, doxazosin, prazosin, terazosin, tamsulosin
- Alpha-blocking antihypertensive agents
- Nitrate derivatives and related compounds
- Baclofen.

Risperidone

Caution should be exercised and the risks and benefits of the combination or co-treatment of risperidone 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).

Levothyroxine
High doses of furosemide can inhibit the binding of thyroid hormones to carrier proteins. This can initially lead to a transient increase in free thyroid hormones, followed by a general decrease in total thyroid hormone levels. The level of thyroid hormones must be monitored.

Combinations to be taken into account

NSAIDs
Non-steroidal anti-inflammatory drugs (e.g. indomethacin and acetylsalicylic acid) can reduce the effect of furosemide. In patients developing hypovolaemia on furosemide therapy or in case of dehydration, concurrent administration of non-steroidal anti-inflammatory drugs (NSAIDs) may induce acute renal failure. Hydrate the patient; monitor renal function at the start of treatment.
The toxicity of high-dosed salicylates can be potentiated in concomitant use of furosemide.

Phenytoin
In concurrent administration of phenytoin, an attenuated effect of furosemide was described (up to 50 %). Higher doses of furosemide may be required.

Aliskiren
Aliskiren lowers the plasma concentration of orally administered furosemide. In patients treated with both aliskiren and oral furosemide it is recommended to monitor for a reduced diuretic effect and adjust the dose accordingly.

Medicinal products causing hypokalaemia
Furosemide can enhance the effect of other hypokalaemic agents, resulting in an increased risk of hypokalaemia. Monitor serum potassium levels and correct if necessary.

Co-administration of furosemide and glucocorticoids, carbenoxolone, liquorice in large amounts, and prolonged use of laxatives, tetracosactide or amphotericin B (IV) may lead to enhanced losses of potassium with the risk of developing hypokalaemia. Hypokalaemia is a factor that promotes the onset of cardiac arrhythmias (particularly *torsades de pointes*) and increases the toxicity of certain active substances, such as digoxin. As a result, active substances that can cause hypokalaemia are involved in a large number of interactions.

Caution should be exercised in concomitant administration of diuretics, potassium-sparing agents, alone or in combination (amiloride, potassium canrenoate, eplerenone, spironolactone, triamterene) as it, does not rule out the occurrence of hypokalaemia or, particularly in patients with renal insufficiency and diabetes, hyperkalaemia.
Monitor serum potassium levels, possibly with an ECG, and reconsider treatment if necessary.

Cardiac glycosides and other medicinal products inducing prolongation of the QT interval
Cardiac glycosides (e.g., digitalis) and other medicinal products which may induce prolongation of the QT interval (e.g., terfenadine, some antiarrhythmic of classes I and III): induced hypokalaemia and/or hypomagnesaemia may potentiate the effect of cardiac glycosides and aggravate the risk of ventricular arrhythmias. See also section 4.4.

Medications that may cause torsades de pointes
Medications that may cause *torsades de pointes*, like class Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide) and class III (amiodarone, sotalol, ibutilide, dofetilide), certain phenothiazine neuroleptics (chlorpromazine, cyamemazine, fluphenazine, levomepromazine, pipotiazine), benzamides (amisulpride, sulpiride, sultopride, tiapride), butyrophenones (droperidol, haloperidol, pipamperone), other neuroleptics (pimozide, sertindole, flupentixol, zuclopenthixol), others: bepridil, cisapride, diphemanil, dolasetron IV, dronedarone, spiramycin IV, erythromycin IV, mizolastine, levofloxacin, halofantrine, lumefantrine, pentamidine, vincamine IV, moxifloxacin, mequitazine, methadone, prucalopride, toremifene, arsenic trioxide, citalopram, escitalopram increase the risk of ventricular arrhythmias, especially *torsades de pointes*.
Correct any hypokalaemia before administering the product and perform clinical, electrolyte, and electrocardiographic monitoring.

Medicinal products causing hyponatraemia

Concomitant administration of diuretics, desmopressin, selective serotonin reuptake inhibitors, oxcarbazepine, carbamazepine or aminoglutethimide may increase the risk of hyponatraemia. See also section 4.4.

Probenecid, methotrexate and other medicinal products with secretion in kidneys
Probenecid, methotrexate and other medicinal products – with like furosemide considerable tubular secretion in the kidneys – can diminish the effect of furosemide. Conversely, furosemide can reduce the renal elimination of probenecid, methotrexate and other medicinal products with like furosemide considerable tubular secretion in the kidneys. In high-dosed treatment (especially with furosemide as well as with other medicinal products), this may lead to elevated serum levels of furosemide or adjuvant medication and a higher risk of side effects.

Antidiabetics and sympathomimetics
The effect of antidiabetics or blood-pressure-increasing sympathomimetics(e.g., epinephrine, norepinephrine) can be attenuated in concomitant use of furosemide.
Lactic acidosis due to metformin, triggered by possible functional renal failure related to diuretics, especially loop diuretics. Do not use metformin when creatinine levels exceed 15 mg/l (135 micromoles/l) in men and 12 mg/l (110 micromoles/l) in women.

Theophylline and curare muscle relaxants
The effect of theophylline or curariform muscle relaxants can be potentiated due to furosemide.

Nephrotoxic antibiotics
Furosemide can enhance the toxic effects of nephrotoxic antibiotics (e.g., aminoglycosides, cephalosporins, polymyxins). Impairment of renal function may develop in patients receiving concurrent treatment with furosemide and high doses of certain cephalosporins.
In case that the use of nephrotoxic antibiotics, such as aminoglycosides, and furosemide can not be avoided, hydration status of the patient and renal function of the patient as well as hearing function should be monitored closely (see also section Medicinal products causing ototoxicity, above).

Ciclosporin A
Concomitant use of ciclosporin A and furosemide is associated with increased risk of gouty arthritis secondary to furosemide-induced hyperuricaemia and ciclosporin impairment of renal uric excretion.

X-ray contrast media
Patients taking furosemide should be rehydrated prior to receiving X-ray contrast media, as diuretics may cause dehydration which increases risk of acute renal impairment especially in cases where patients are given high doses of contrast media.
In patients at high risk for radiocontrast nephropathy, furosemide led to a higher incidence of deterioration in renal function after receiving X-ray contrast media compared to high-risk patients who received only intravenous hydration prior to receiving X-ray contrast media.

4.6 Fertility, pregnancy and lactation

Pregnancy
Furosemide is to be used during pregnancy only for a short-term period and after especially strict diagnosis, since furosemide crosses the placenta.

Diuretics are not suitable for routine therapy of hypertension and oedemas during pregnancy, since they impair placental perfusion and consequently intrauterine growth.

If furosemide must be used in case of cardiac or renal insufficiency of the pregnant woman, careful monitoring of electrolytes and haematocrit as well as of foetal growth is required. Displacement of bilirubin from albumin binding and thus elevated risk of nuclear icterus in hyperbilirubinemia is discussed for furosemide.

No malformations in humans which might be associated with exposure to furosemide have been reported to date. However, there is insufficient experience to allow a concluding evaluation of a potential damaging effect in the embryo/foetus. Animal studies have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Furosemide Clonmel should not be used in pregnant women unless the benefits to the patient outweigh the possible risk to the foetus which includes persistence of patent *ductus arteriosus* (section 4.8).

Breast-feeding

Furosemide pass into the breast milk and may inhibit lactation. Breast-feeding is contraindicated during treatment with furosemide (see section 4.3).

Fertility
No human data on the effect of furosemide on fertility are available.

4.7 Effects on ability to drive and use machines

In some patients dizziness or fatigue may occur at the beginning of treatment or when increasing the dose, due to decrease in blood pressure, which can affect the ability to drive and operate machinery. Patients should be advised to not drive or operate machinery if any of the above occurs.

4.8 Undesirable effects

The frequencies of adverse effects are derived from literature data referring to clinical studies in which furosemide was used in a total of 1387 patients, across all doses and indications. When the frequency category for the same adverse effect differs, the highest frequency category was chosen.

Frequencies are defined in accordance with current guidance, as:
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
Common: Haemoconcentration (in case of excessive diuresis) [1].
Uncommon: Thrombocytopenia.
Rare: Eosinophilia, leucopenia.
Very rare: Haemolytic anaemia, aplastic anaemia, agranulocytosis [2].

Immune system disorders
Rare: Severe anaphylactic and anaphylactoid reactions such as anaphylactic shock (for treatment see section 4.9).
Not known: Exacerbation or activation of systemic lupus erythematosus.

Metabolism and nutrition disorders
Very common: Electrolyte disturbances (including symptomatic) [3], dehydration and hypovolaemia (particularly in elderly patients) [1,3], blood creatinine increased [4], blood triglyceride increased [4].
Common: Hyponatraemia (see sections 4.4. and 4.9) and hypochloraemia, hypokalaemia (see sections 4.2, 4.4 and 4.9) [5], blood cholesterol increased [4], hyperuricemia and attacks of gout [4].
Uncommon: Glucose tolerance impaired and hyperglycaemia [6]. Latent diabetes mellitus may become manifest (see section 4.4).
Not known: Hypocalcaemia, hypomagnesaemia, blood urea increased [4], metabolic alkalosis, Pseudo-Bartter syndrome (in association with abuse and/or long-term treatment with furosemide) [7].

Nervous system disorders
Common: Hepatic encephalopathy in patients with hepatic insufficiency (see section 4.3 and 4.4).
Rare: Paraesthesia.
Not known: Dizziness, fainting and loss of consciousness (caused by symptomatic hypotension), headache.

Ear and labyrinth disorders
Uncommon: Hearing disorders, deafness [8] (sometimes irreversible).
Rare: Tinnitus [8].

Vascular disorders
Very common: Hypotension, including orthostatic hypotension (see section 4.4).
Rare: Vasculitis.
Not known: Thrombosis (particularly in elderly patients) [1].

Gastrointestinal disorders
Uncommon: Nausea.
Rare: Vomiting, diarrhoea.
Very rare: Acute pancreatitis.

Hepatobiliary disorders
Very rare: Cholestasis, increase in hepatic transaminases.

Skin and subcutaneous tissue disorders
Uncommon: Allergic or non-allergic skin reactions, rash, pruritus, urticaria, dermatitis bullous, erythema multiforme, bullous pemphigoid, dermatitis exfoliative, purpura, photosensitivity (see section 4.4).
Not known: Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS), lichenoid reactions.

Musculoskeletal and connective tissue disorders
Not known: Rhabdomyolysis (in association with severe hypokalaemia).

Renal and urinary disorders
Common: Increased urine volume [9]
Rare: Tubulointerstitial nephritis.
Not known: Urine sodium increased, urine chloride increased, symptoms of urinary outflow obstruction, nephrocalcinosis /nephrolithiasis in premature infants (see section 4.4) [10], renal failure (see section 4.5).

Congenital, familial and genetic disorders
Not known: Increased risk of persistence of patent ductus arteriosus Botalli when furosemide is administered to premature infants during the first weeks of life.

General disorders and administration site conditions
Rare: Fever.

[1] Hypovolaemia and dehydration may lead, particularly in elderly patients, to frequent haemoconcentration with a risk of thrombosis (frequency not known).
[2] Typical signs of agranulocytosis include fever with chills, sore throat, changes of the mucous membranes.
[3] Very common electrolyte disturbances (particularly common hypokalaemia and/or hyponatraemia), dehydration, hypovolaemia very commonly accompanied by orthostatic hypotension and metabolic alkalosis (frequency not known) may be observed in relation to the activity of the product, justifying discontinuation of the medication or reduction of the dosage. These electrolyte disturbances are exacerbated by an overly strict low-sodium diet, certain medical conditions (e.g. cirrhosis, heart failure), concomitant use of other medicinal products, and digestive and nutritional disorders, which can aggravate hypokalaemia in particular.
[4] Treatment with furosemide may cause a transient, very common increase in serum creatinine and blood urea (frequency not known), as well as a common increase in cholesterol and a very common increase in blood triglycerides. A slight increase in uric acid levels (in the range of 10 to 30 mg/l) may commonly occur during treatment and promote an attack of gout.
[5] Hypokalaemia may or may not be associated with metabolic alkalosis. It occurs more readily with the use of high doses or in patients with cirrhosis, malnutrition or heart failure. Hypokalaemia can be particularly serious in patients with heart failure and can also cause severe arrhythmias, particularly *torsades de pointes* (which can be fatal), especially when combined with quinidine-type antiarrhythmics (see section 4.5).
[6] An increase in blood glucose levels is sometimes observed, most often during intense and short-term administration, particularly intravenously. Decreased glucose tolerance has been reported uncommonly. In cases of diabetes, loss of blood glucose control may occur.
[7] Pseudo-Bartter syndrome (which includes hypokalaemia, hypochloraemia, alkalosis and hyperaldosteronism) may occur in the context of misuse and/or long-term use of the product (frequency not known).
[8] Uncommon hearing disorders and rare cases of tinnitus, usually transient, may occur, particularly in patients with renal insufficiency or hypoproteinaemia (e.g., in nephrotic syndrome) (see section 4.4). Cases of deafness, sometimes irreversible, have been reported uncommonly after oral or intravenous administration of the product. Uncommon cases of hearing disorders have been reported during concomitant administration of aminoglycoside antibiotics.
[9] Common increases in diuresis may cause or aggravate urinary retention (frequency not known) in patients with obstruction and/or compression of the urinary tract.
[10] Cases of nephrocalcinosis and/or intrarenal lithiasis (frequency not known) associated with hypercalciuria have been observed in very premature infants treated with high doses of injectable furosemide.

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 HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Symptoms
The clinical picture of an acute or chronic overdose depends on the extent of the water and electrolyte losses. Overdose may lead to hypotension, orthostatic dysregulations, electrolyte disturbances (hypokalaemia, hyponatraemia, hypochloraemia) or alkalosis. Major loss of fluid can result in marked hypovolaemia, dehydration, circulatory collapse and haemoconcentration with diathesis to thrombosis. Delirious states may occur in connection with rapid losses of water and electrolytes.
An anaphylactic shock is rare (symptoms: increased sweating, nausea, cyanosis, pronounced drop in blood pressure, depression of consciousness up to coma etc).

Management
Overdose or signs of hypovolaemia (hypotension, orthostatic dysregulations) necessitate immediate discontinuation of treatment with furosemide.

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 impaired micturition (e.g., patients with prostatic hyperplasia), unrestricted urinary outflow must be ensured, since sudden polyuria can lead to ischuria accompanied by hyperextension of the bladder.

Therapy in cases of hypovolaemia: volume substitution.
Therapy in cases of hypokalaemia: potassium substitution.
Therapy in circulatory collapse: shock positioning; if necessary, shock therapy.

Emergency measures in case of anaphylactic shock
At the first signs (sweating, nausea, cyanosis), a venous channel should be inserted. In addition to other usual emergency measures, Trendelenburg position (head chest down position) and clear airways should be ensured.

Medical emergency measures:

- *Immediately: intravenous administration of adrenaline,*

there is a possibility of cardiac arrhythmia. The administration of adrenaline can be repeated (observe the instructions for use of adrenaline!).

- *Then intravenous administration of glucocorticoids follows*

e.g. 250-1000 mg prednisolone (or an equivalent amount of one of the derivatives). The administration of glucocorticoids can be repeated (observe the instructions for use of glucocorticoids!).

- *Then intravenous volume substitution*

e.g. plasma expander, human albumin, electrolyte solution.

Further therapeutic measures:
Artificial respiration, oxygen inhalation, antihistamines.
In case of cardiac arrest, reanimation according to current recommendations.
The doses given are for adults of normal weight; in children the dose should be adjusted according to their body weight.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diuretics, sulfonamides, plain, ATC code: C03CA01

Mechanism of action
Furosemide is a potent, short and rapid-acting loop diuretic. It inhibits the re-absorption of $Na^+/2Cl^-/K^+$ in the ascending part of Henle's loop by blocking the ion carrier for these ions. The fractional sodium excretion can amount to 35 % of the glomerularly filtrated sodium. Increased sodium excretion leads secondarily to increased urinary excretion and to increased distal-tubular K^+-secretion attributable to osmotically bound water. The excretion of Ca^{2+} and Mg^{2+} ions is also increased. Besides the losses of the above-mentioned electrolytes, excretion of uric acid may be reduced, and a shift of the acid-base balance towards metabolic alkalosis may occur. Furosemide interrupts the tubuloglomerular feedback mechanism at the *macula densa*, so that the saluretic efficacy is not attenuated.
Furosemide increases renal blood flow to the cortical zone. This property is particularly useful when combined with beta-blockers, which may have the opposite effect.
It does not alter glomerular filtration (although an increase in glomerular filtration has been observed in certain circumstances). The salidiuretic action increases in proportion to the dose administered and persists in cases of renal impairment.
It has a haemodynamic action characterised by a decrease in pulmonary capillary pressure even before the onset of diuresis, and by an increase in the storage capacity of the venous vascular bed as demonstrated by plethysmography (these properties have been studied more specifically by IV administration).

Pharmacodynamic effects
Furosemide leads to dose-dependent stimulation of the renin-angiotensin-aldosterone system. In case of cardiac insufficiency, furosemide leads to an acute reduction of the cardiac preload through dilatation of the venous capacitance vessels. This early vascular effect seems to be mediated through prostaglandins and requires sufficient renal function with activation of the renin-angiotensin aldosterone system as well as intact prostaglandin synthesis.

Furosemide has an antihypertensive effect as a consequence of increased excretion of sodium chloride and reduced responsiveness of vascular smooth muscle cells to vasoconstrictive stimuli, and a reduction in blood volume.

5.2 Pharmacokinetic properties

Absorption
Furosemide is rapidly but incompletely absorbed (60-70 %) on oral administration Maximum plasma concentration is reached in approximately 60 minutes. Absorption is slowed but not reduced by the presence of food.
In patients with chronic heart failure or nephrotic syndrome, absorption may be reduced to less than 30 %.

Distribution and biotransformation
96 to 98 % of furosemide is bound to plasma albumin and little biotransformation takes place.
Protein binding is reduced in patients with renal and hepatic impairment.
The apparent volume of distribution is approximately 0.2 l/kg body weight (0.8 l/kg body weight in neonates).

A small portion of resorbed furosemide is inactivated by hepatic and probably renal glucuronidation.

Elimination
The elimination half-life is about 1 hour in normal renal function; in terminal renal failure it increases to about 24 hours.

Furosemide crosses the placental barrier.

Furosemide passes into breast milk.

Special populations

Elderly
The elimination of furosemide is delayed in the elderly where a certain degree of renal impairment is present.

Paediatric population
New-borns
Bioavailability after oral administration is reduced.

- Full-term newborns: the plasma half-life is prolonged (up to 7 hours) because the apparent volume of distribution is increased and plasma clearance is reduced.

- In premature infants: the plasma half-life may reach 20 hours due to reduced urinary excretion of the diuretic.

5.3 Preclinical safety data

Single dose toxicity
Single dose toxicity (LD_{50}) has been studied in different animal species. In mice and rats, the oral LD_{50} of furosemide is between 1 050 mg/kg and 4 600 mg/kg bw, and in budgerigars 243 mg/kg. In dogs, the oral LD_{50} is approximately 2 000 mg/kg bw, and the intravenous LD_{50} is more than 400 mg/kg.

Repeated dose toxicity
Repeated dose toxicity studies have been carried out in rats and dogs, among others. In both species, renal changes (including focal fibrosis, calcification of the kidneys) occurred in groups receiving high doses (10 to 20 times the therapeutic dose for humans) after 6-12 months of use.

Mutagenic and tumorigenic potential
There are both positive and negative test results for furosemide in bacteria and mammalian cells *in vitro*. Induction of gene and chromosome mutations was only observed in the cytotoxic range of concentrations.

Toxic effect on reproductive capacity
Furosemide crosses the placenta and reaches 100 % maternal serum concentration in the umbilical cord blood. To date, there are no known deformities in humans that may be related to furosemide exposure. However, there are insufficient results to conclusively assess the potential adverse effects on the embryo/foetus. In the foetus, furosemide may stimulate urine production *in utero*. During treatment urolithiasis has been observed in premature infants treated with furosemide.

Studies in newborn rats treated with 75 mg furosemide per kg body weight from days 7 to 11 and 14 to 18 of gestation showed a reduced number of differentiated glomeruli.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Pregelatinised maize starch
Sodium starch glycolate (Type A)
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Furosemide Clonmel 20 mg tablets
Blister: 2 years.
Bottle: 2 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

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

6.5 Nature and contents of container

Furosemide Clonmel 20 mg tablets is packed in:
PVDC/PVC//Alu blisters containing 30, 50, 100 tablets or

PVDC/PVC//Alu perforated unit dose blisters containing 30x1 tablet or
HDPE bottles with screw cap containing 100, 250, 500, 1000 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel, Co. Tipperary
E91 D768
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/421/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th May 2026

10 DATE OF REVISION OF THE TEXT