SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Furosemide 40mg Tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 40mg furosemide.
For excipients, see 6.1

3. PHARMACEUTICAL FORM

Tablet.

Appearance: A white, circular, flat bevelled edge tablet with ‘F’ scoreline 40’ embossed on one face and plain on the reverse.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

In the treatment of oedema associated with congestive heart failure, cirrhosis of the liver, renal disease including nephrotic syndrome.

In the treatment of peripheral oedema due to mild to moderate hypertension (alone, or in combination with other antihypertensive agents in the treatment of more severe cases).

Management of oliguria due to acute or chronic renal insufficiency.

4.2. Posology and method of administration

Adults: The usual initial daily dose is 40mg. This may require adjustment until the effective dose is achieved. In mild cases 20mg daily or 40mg on alternate days may be sufficient, whereas in cases of resistant oedema daily doses of 80mg and above may be used.
In patients with chronic renal insufficiency, an initial daily dose of 250mg is employed. If a satisfactory diuresis is not produced then the dose may be increased in steps of 250mg at four to six hourly intervals up to a maximum daily dose of 1,500 mg in 24 hours. In exceptional cases up to 2,000 mg in 24 hours may be given.

Children: The oral dose for children ranges from 1-3mg/kg body weight daily, up to a maximum total dose of 40mg per day.

Elderly: The usual adult dose, but caution is advised as furosemide is excreted more slowly in the elderly.

Method of administration: Oral – the tablets should be swallowed with water.

4.3 Contraindications

- Hypersensitivity to furosemide, any of its excipients, sulphonamides, sulphonamide derivatives/amiloride
- Anuria and impaired renal function (creatinine clearance below 30mL/min per 1.73 m2 body surface area) and renal failure resulting from poisoning by nephrotoxic and/or hepatotoxic agents
- Electrolyte disturbances (severe hyponatraemia: severe hypokalaemia, hypovolaemia), dehydration and/or hypotension (see section 4.4)
- Concomitant potassium supplements or potassium sparing diuretics (see section 4.5)
- Pre-coma/coma associated with hepatic cirrhosis or encephalopathy
- Addison's disease
- Digitalis intoxication (see also section 4.5)
- Breast-feeding women (see section 4.6)

4.4 Special warnings and precautions for use

Hypotension and/or hypovolaemia (see also section 4.3)

These and any acid-base disturbances should be corrected before furosemide is started.

Dose titration/adjustment (see section 4.2)
Patients with hypoproteinaemia (such as that associated with the nephrotic syndrome) require careful dose titration (reduced furosemide effect: increased risk of ototoxicity)

In moderate liver congestion dosage adjustment may be needed.

**Caution required:**

Use with caution in following circumstances
- impaired hepatic function (see sections 4.3 and below – monitoring required)
- impaired renal function and hepato-renal syndrome (see section 4.3 and below – monitoring required)
- diabetes mellitus (latent diabetes may become overt: insulin requirements in established diabetes may increase) or adrenal disease.

- elderly patients
- difficulty with micturition/potential obstruction in the urinary tract including prostatic hypertrophy (increased risk of acute retention).

- gout (increased risk of hyperuricaemia)
- patients at risk of pronounced falls in blood pressure.

*Clinical monitoring requirements (see also section 4.8):*

Regular monitoring for
- blood dyscrasias. If these occur, stop furosemide immediately
- liver damage
- idiosyncratic reactions.

In premature infants there is a risk of development of nephrocalcinosis/nephrolithiasis. Renal function must be monitored and renal ultrasonography performed.

*Laboratory monitoring requirements:*

- frequent BUN (blood urea nitrogen test) in first few months of treatment, periodically thereafter
- serum electrolytes with replacement as appropriate.

*Other alterations in lab values*

- Serum creatinine and urea levels tend to rise during treatment
- Serum cholesterol and triglycerides may rise but usually return to normal within 6 months of starting furosemide
- Furosemide should be discontinued before a glucose tolerance test
This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

**Cardiac glycosides** – hypokalaemia and electrolyte disturbances (including magnesium) increases the risk of cardiac toxicity.

**Antihypertensives** – enhanced hypotensive effect possible with all types. Concurrent use with ACE inhibitors can result in marked falls in blood pressure. Furosemide should be stopped or the dose reduced before starting an ACE-inhibitor. There is a risk of a first-dose effect with post-synaptic alphablockers eg prazosin. Furosemide may interact with ACE inhibitors causing impaired renal function.

**Antibiotics** – The nephrotoxic effect of cefaloridine and the aminoglycoside antibiotics may be increased by furosemide. Increased risk of ototoxicity with aminoglycosides, polymixins or vancomycin. Furosemide can decrease vancomycin serum levels after cardiac surgery.

**NSAIDs** – The action of diuretics such as furosemide may be antagonised by certain non-steroidal anti-inflammatory agents like Indometacin and ketorolac. Also increased risk of nephrotoxicity (especially if there is hypovolaemia). In patients with dehydration or hypovolaemia, NSAIDs may cause acute renal insufficiency.

**Lithium** - The renal clearance of lithium is decreased by furosemide, resulting in increased and possibly toxic serum levels. Concomitant administration should be avoided unless plasma levels can be monitored.

**Corticosteroids** – Concurrent administration of glucocorticoids may cause sodium retention and exacerbate potassium loss.

**Antidiabetics** - hypoglycaemic effects antagonised by furosemide.

**Insulin** - requirements may be increased (see section 4.4).

**Salicylates** - effects may be potentiated by furosemide.

**Theophylline** - enhanced hypotensive effect

**Muscle relaxants** - enhanced hypotensive effect with baclofen or tizanidine (see also Anaesthetic agents below – curare).
Antihistamines – hypokalaemia with increased risk of cardiac toxicity.

Anti-arrhythmics - (including amiodarone, disopyramide, flecanaide and sotalol) - risk of cardiac toxicity (because of furosemide-induced hypokalaemia). The effects of lidocaine, tocainide or mexiletine may be antagonised by furosemide.

Drugs associated with QT prolongation – cardiac toxicity may be increased by furosemide-induced hypokalaemia and/or hypomagnesaemia.

Vasodilators – enhanced hypotensive effect with moxisylyte (thymoxamine) or hydralazine.

Renin inhibitors – aliskiren reduces plasma concentrations of furosemide.

Nitrates – enhanced hypotensive effect.

Antipsychotics – furosemide-induced hypokalaemia increases the risk of cardiac toxicity. Avoid concurrent use with pimozide. Increased risk of ventricular arrhythmias with amisulpride or sertindole. Enhanced hypotensive effect with phenothiazines.

Chelating agents – sucralfate may decrease the gastro-intestinal absorption of furosemide – the 2 drugs should be taken at least 2 hours apart.

Lipid regulating drugs – Bile acid sequestrants (eg colestyramine; colestipol) – reduced absorption of furosemide – administer 2 to 3 hours apart.

Antidepressants – enhanced hypotensive effect with MAOIs. Increased risk of postural hypotension with TCAs (tricyclic antidepressants). Possible increased risk of hypokalaemia with reboxetine.

Antiepileptics – increased risk of hyponatraemia with carbamazepine. Diuretic effect reduced by phenytoin.

Antifungals – increased risk of hypokalaemia with amphotericin.

Anxiolytics and hypnotics – enhanced hypotensive effect. Chloral or triclorflos may displace thyroid hormone from binding site.

CNS stimulants (drugs used for ADHD) – hypokalaemia increases the risk of ventricular arrhythmias.

Cytotoxics – increased risk of nephrotoxicity and ototoxicity with platinum compounds.

Other diuretics – profound diuresis possible when furosemide given with metolazone. Increased risk of hypokalaemia with thiazides.

Dopaminergics – enhanced hypotensive effect with levodopa.

Immunomodulators – enhanced hypotensive effect with aldesleukin.

Oestrogens and progestogens – diuretic effect antagonised.
**Prostaglandins** – enhanced hypotensive effect with alprostadil.

**Sympathomimetics** – increased risk of hypokalaemia with high doses of beta_2_ sympathomimetics (such as bambuterol, femoterol, salbutamol, salmeterol and terbutaline).

**Probenecid** – reduced renal clearance of furosemide and decreased diuretic effect.

**Anaesthetic agents** – general anaesthetic agents may enhance the hypotensive effects of furosemide. The effects of curare may be enhanced by furosemide.

**Alcohol** – enhanced hypotensive effect.

**Laxative abuse** - increases the risk of potassium loss.

**Liquorice** - excess intake may increase the risk of hypokalaemia.

### 4.6. Pregnancy and lactation

The teratogenic and embryotoxic potential of furosemide in humans is unknown. There is little evidence of safety of high-dose furosemide in human pregnancy, although the results of animal work, in general, show no hazardous effects.

The drug 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).

As it may inhibit lactation and passes into breast milk, furosemide should be used with caution in nursing mothers.

### 4.7. Effects on ability to drive and use machines

Reduced mental alertness and rarely dizziness and blurred vision have been reported. Patients so affected should not drive or operate machines.

### 4.8. Undesirable effects

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); Frequency not known (cannot be estimated from the available data).

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders:</th>
<th>Uncommon:</th>
<th>aplastic anaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare:</td>
<td>bone marrow depression (necessitates withdrawal of treatment), eosinophilia, leucopenia.</td>
<td></td>
</tr>
<tr>
<td>Very rare:</td>
<td>haemolytic anaemia, agranulocytosis, thrombocytopenia, vasculitis.</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutritional disorders:</td>
<td>Very common: dehydration, hyponatraemia, hypochloremic metabolic alkalosis, hypocalcaemia, hypomagnesemia (incidences of the last three are reduced by triamterene), nephrocalcinosis in infants</td>
<td></td>
</tr>
<tr>
<td>Common:</td>
<td>Hypovolaemia, hypochloraemia</td>
<td></td>
</tr>
<tr>
<td>Uncommon:</td>
<td>impaired glucose tolerance (by hypokalaemia) hyperuricaemia, gout, reduction of serum HDL-cholesterol, elevation of serum LDL-cholesterol, elevation of serum triglycerides, hyperglycaemia</td>
<td></td>
</tr>
<tr>
<td>Very rare:</td>
<td>tetany</td>
<td></td>
</tr>
<tr>
<td>Frequency not known:</td>
<td>aggravated pre-existing metabolic alkalosis (in decompensated cirrhosis of the liver), fluid and electrolyte disturbances, hyperglycaemia.</td>
<td></td>
</tr>
</tbody>
</table>

| Psychiatric disorder: | Rare: psychiatric disorder NOC |

| Nervous system disorders: | Rare: paraesthesia, confusion, headache, dizziness. |

| Eye disorders: | Uncommon: visual disturbance, blurred vision, yellow vision. |

| Ear and labyrinth disorders: | Rare: tinnitus and reversible or irreversible loss of hearing (although usually transitory, particularly in patients with renal failure, hypoproteinaemia (e.g. in nephritic syndrome) |

| Cardiac disorders: | Uncommon: orthostatic intolerance, cardiac arrhythmias, increased risk or persistence of patent ductus arteriosus in premature infants. |

| Vascular disorders: | Very common: decreased blood pressure, (which, if pronounced may cause signs and symptoms such as impairment of concentration and reactions, light-headedness, sensations of pressure in the head, headache, dizziness, drowsiness, weakness, disorders of vision, dry mouth, orthostatic intolerance). |
| Uncommon: | hypotension, hypovolaemia |
| Rare: | vasculitis, thrombosis, shock |

| Gastrointestinal disorders: | Uncommon: dry mouth, thirst, nausea, bowel motility disturbances, vomiting, diarrhoea, constipation |
| Rare: | acute pancreatitis (in long-term diuretic treatment, including furosemide). |

| Hepatobiliary disorders: | Rare: pure intrahepatic cholestasis (jaundice), hepatic function abnormal. |

| Skin and subcutaneous tissue disorders: | Rare: rash, pruritus, photosensitivity, toxic epidermal necrolysis. |
| Frequency not known: | urticaria, erythema multiforme, purpura, exfoliative dermatitis, itching, allergic reactions, such as skin rashes, various |
forms of dermatitis including urticaria, bullous lesions. When these occur treatment should be withdrawn.

| Musculoskeletal and connective tissue disorders: | Uncommon: | muscle cramps, muscle weakness. |
| | Rare: | nephrocalcinosis (in pre-term infants treated with Furosemide), interstitial nephritis, acute renal failure. |
| Congenital, familial and genetic disorders: | Rare: | patent ductus arteriosus |
| General disorders and administration site conditions: | Uncommon: | Fatigue |
| | Rare: | malaise, fever, severe anaphylactoid or anaphylactic reactions (e.g. with shock). |
| | Frequency not known: | hypovolaemia, |
| Investigations: | Common: | creatinine increased, blood urea increased |
| | Rare: | Transaminases increased, blood |

**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; website: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard)

### 4.9 Overdose

In cases of overdosage there is a danger of dehydration and electrolyte depletion due to excessive diuresis. In cirrhotic patients, overdosage may precipitate hepatic coma. Treatment should be aimed at fluid replacement and correction of electrolyte imbalance. Gastric lavage may be useful if ingestion is recent.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

ATC code: CO3C A01

The evidence from many experimental studies suggests that furosemide acts along the entire nephron with the exception of the distal exchange site. The
main effect is on the ascending limb of the loop of Henley with a complex effect on renal circulation. Blood-flow is diverted from the juxta-medullary region to the outer cortex.

The principle renal action of furosemide is to inhibit active chloride transport in the thick ascending limb. Re-absorption of sodium chloride from the nephron is reduced and a hypotonic or isotonic urine produced.

It has been established that prostaglandin (PG) biosynthesis and the renin-angiotensin system are affected by furosemide administration and that furosemide alters the renal permeability of the glomerulus to serum proteins.

5.2 Pharmacokinetic properties

Furosemide is a weak carboxylic acid which exists mainly in the dissociated form in the gastrointestinal tract. Furosemide is rapidly but incompletely absorbed (60-70%) on oral administration and its effect is largely over within 4 hours. The optimal absorption site is the upper duodenum at pH 5.0. Regardless of route of administration 69-97% of activity from a radio-labelled dose is excreted in the first 4 hours after the drug is given. Furosemide is bound to plasma albumin and little biotransformation takes place. Furosemide is mainly eliminated via the kidneys (80-90%); a small fraction of the dose undergoes biliary elimination and 10-15% of the activity can be recovered from the faeces.

In renal/hepatic impairment
Where liver disease is present, biliary elimination is reduced up to 50%. Renal impairment has little effect on the elimination rate of furosemide, but less than 20% residual renal function increases the elimination time.

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

New born
A sustained diuretic effect is seen in the newborn, possibly due to immature tubular function.

5.3 Preclinical safety data

Not relevant

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate  
Magnesium stearate (E470b)  
Sodium starch glycollate  
Maize starch.  
Starch paste 15%

6.2. Incompatibilities

Not Applicable

6.3. Shelf life

Tablet container: 5 Years  
Blister: 2 Years

6.4. Special precautions for storage

Tablet containers: Do not store above 25°C. Store in the original container. Keep the container tightly closed.  
Blister packs: Do not store above 25°C. Store in the original package.

6.5. Nature and contents of container

Tablet container and cap (polypropylene container with low density polyethylene cap)  
Pack sizes: 28, 56, 100, 250, 500, 1000 and 1008 tablets.  
Blister (250 (µm white opaque PVC and 20 (µm hard temper aluminium foil).  
Pack sizes: 28, 56 and 1008 tablets.

6.6. Instruction for use and handling (, and disposal)

Not applicable

7 MARKETING AUTHORISATION HOLDER

Aurobindo Pharma Limited  
Ares,
8. MARKETING AUTHORISATION NUMBER

PL 20532/0040

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/10/2005

10. DATE OF REVISION OF THE TEXT

08/03/2016