Public Assessment Report

Furosemide 20mg Tablets
Furosemide 40mg Tablets

PL 13606/0116
PL 13606/0117

Co-Pharma Limited

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Lay Summary

The MHRA granted Co-Pharma Limited Marketing Authorisations (licences) for the medicinal products Furosemide 20mg Tablets (PL 13606/0116) and Furosemide 40mg Tablets (PL 13606-0117) on 2nd August 2006.

These products contain the active ingredient furosemide which is a diuretic and is used in the treatment of heart failure, hypertension and oliguria.

No new or unexpected safety concerns arose from these simple applications and it was judged, therefore that the benefits of taking Furosemide 20mg and 40mg Tablets outweigh the risks, hence Marketing Authorisations were granted.
SCIENTIFIC DISCUSSION

1. INTRODUCTION

This Public Assessment Report is based on the National Assessment Report for the recently granted Market Authorisations for Furosemide 20mg Tablets (PL 13606/0116) and Furosemide 40mg Tablets (PL 13606/0117). These applications were ‘informed consent’ applications (Article 10.1 (a)(i) Directive 2001/83/EC) for tablets containing 20 mg and 40 mg of the active ingredient furosemide, and were claimed to be identical to Furosemide Tablets BP 20mg and 40mg PL’s 00790/0005, which were granted to Clonmel Healthcare Limited on 09/08/79.

Furosemide is a diuretic and is indicated in the treatment of oedema associated with congestive heart failure, cirrhosis of the liver, renal disease including nephrotic syndrome. It is also indicated 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 and in the management of oliguria due to acute or chronic renal insufficiency.

The product names (Furosemide 20 mg Tablets and Furosemide 40 mg Tablets) are in line with current requirements. The products are tablets containing 20mg and 40mg of the active ingredient furosemide for oral administration. The container and packaging are in line with current requirements. These products are subject to a medical prescription.

2. COMPOSITION

The qualitative composition of the products is given in the table below.

<table>
<thead>
<tr>
<th>Furosemide</th>
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<tbody>
<tr>
<td>Lactose monohydrate</td>
</tr>
<tr>
<td>Maize starch</td>
</tr>
<tr>
<td>Starch paste 15% w/w</td>
</tr>
<tr>
<td>Magnesium stearate</td>
</tr>
<tr>
<td>Sodium starch glycollate</td>
</tr>
<tr>
<td>Maize starch</td>
</tr>
</tbody>
</table>

3. METHOD OF PREPARATION

The method of manufacture is stated to be identical to that of the referenced licences and no particular concerns therefore arise. A valid Manufacturing licence is supplied.

4. CONTROL OF STARTING MATERIALS

4.1 Active Substance

A current Certificate of Suitability for furosemide was supplied.
4.2 Other Ingredients

The qualitative and quantitative composition is identical to the referenced licences. Excipients comply with relevant pharmacopoeial monographs.

5. CONTROL TESTS ON INTERMEDIATE PRODUCTS/FINISHED MEDICINAL PRODUCT & STABILITY

The applicant has consent to refer to the data supporting the marketing authorisations for the reference products. The pharmaceutical expert has confirmed that these are identical for the product intended for marketing. The finished product specification, product shelf-life and storage conditions have been assessed in relation to the reference products. These are satisfactory. The declared product shelf-lives of 2 years (blister packs) and 3 years (containers) are consistent with the reference products.

6. EXPERT REPORT

The pharmaceutical expert report states that the proposed product is identical to the furosemide 20 mg and 40 mg tablets (PL 00790/0005-6) licensed by Clonmel Healthcare Limited.

A clinical expert report has also been provided and states that all details specified are in line with the reference product licenses. A non-clinical expert report has also been provided stating that the non-clinical details are also in line with the reference product licenses.

7. SUMMARY OF PRODUCT CHARACTERISTICS

The SPC’s underwent minor modifications and are now consistent with those of the reference product.

8. PATIENT INFORMATION LEAFLET

The PIL’s underwent minor modifications and are now consistent with those of the reference product.

9. LABELLING

The labelling meets current requirements and is satisfactory.
PRE-CLINICAL ASSESSMENT
No new pre-clinical data were supplied and none were required for this simple application.

CLINICAL ASSESSMENT
No new clinical data were supplied and none were required for this simple application.

CONCLUSION
A marketing authorisation was granted.
OVERALL CONCLUSION AND RISK/BENEFIT ANALYSIS

Quality

The data for these applications are consistent with that previously assessed for the cross-reference product and as such has been judged to be satisfactory.

Preclinical

No new preclinical data were submitted and none are required for applications of this type.

Efficacy

No new efficacy data for were submitted and none are required for this type of application.

Risk Benefit Assessment

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s products are identical to the cross-reference products which, in turn, have been shown to be interchangeable with the innovator products. Extensive clinical experience with furosemide is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.
### STEPS TAKEN DURING ASSESSMENT

<table>
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<th>Description</th>
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<tr>
<td>1</td>
<td>The MHRA received the application on 2\textsuperscript{nd} June 2004.</td>
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<tr>
<td>2</td>
<td>Following initial assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 4\textsuperscript{th} February 2005, 12\textsuperscript{th} January 2006 and 20\textsuperscript{th} March 2006.</td>
</tr>
<tr>
<td>3</td>
<td>The applicant provided further information in regard to the quality assessment on 15\textsuperscript{th} September 2005 and 17\textsuperscript{th} March 2006.</td>
</tr>
<tr>
<td>4</td>
<td>The application was determined on 2\textsuperscript{nd} August 2006.</td>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Furosemide 20 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 20 mg Furosemide

For excipients see 6.1

3 PHARMACEUTICAL FORM
Tablet.

Appearance: White, circular, flat bevelled edge tablet with a breakline on one side.

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
For oral use. The tablets should be swallowed with water.

Adults:

The usual initial daily dose is 40 mg. This may require adjustment until the effective dose is achieved. In mild cases 20 mg daily or 40 mg on alternate days may be sufficient, whereas in cases of resistant oedema daily doses of 80 mg and above may be used as one or two doses daily, or intermittently. Severe cases may require gradual titration of the furosemide dosage up to 600mg.
In patients with chronic renal insufficiency, an initial daily dose of 250 mg is employed. If a satisfactory diuresis is not produced then the dose may be increased in steps of 250 mg 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 – 3 mg/kg body weight daily, up to a maximum total dose of 40 mg per day.

*Elderly:*

The usual adult dose, but caution is advised as furosemide is excreted more slowly in the elderly. Dosage should be titrated until the required response is achieved.

### 4.3 CONTRAINDICATIONS

Furosemide is contra-indicated in patients with hypovolaemia or dehydration, anuria or renal failure with anuria not responding to furosemide, renal failure as a result of poisoning by nephrotoxic or hepatotoxic agents or renal failure associated with hepatic coma, severe hypokalaemia, severe hyponatraemia, pre-comatose and comatose states associated with hepatic encephalopathy and breast feeding women.

Hypersensitivity to furosemide or any of the excipients. Patients allergic to sulphonamides may show cross-sensitivity to furosemide.

### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Too vigorous diuresis may cause orthostatic hypotension or acute hypotensive episodes.

Where indicated, steps should be taken to correct hypotension or hypovolaemia before commencing therapy.

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. Hypovolaemia or dehydration as well as any significant electrolyte and acid-base disturbances must be corrected. This may require temporary discontinuation of furosemide.
Urinary output must be secured. Patients with partial obstruction of urinary outflow, for example patients with prostatic hypertrophy or impairment of micturition, have an increased risk of developing acute retention and require careful monitoring.

Particularly careful monitoring is necessary in:

- Patients with hypotension.
- Patients who are at risk from a pronounced fall in blood pressure.
- Patients with latent or manifest diabetes. Furosemide may necessitate adjustment of control by hypoglycaemic agents in cases of diabetes mellitus.
- Patients with gout.
- Patients with hepatorenal syndrome.
- Patients with hypoproteinaemia, e.g. associated with nephritic syndrome (the effect of furosemide may be weakened and its ototoxicity potentiated). Cautious dose titration is required.
- Premature infants (possible development nephrocalcinosis/nephrolithiasis; renal function must be monitored and renal ultrasonography performed).

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

### 4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

The concomitant administration of this preparation with cardiac glycosides or hypotensive agents may necessitate adjustment of the dosage of those drugs.

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

Impairment of renal function may develop in patients receiving treatment with furosemide and high doses of certain cephalosporins.

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.

Corticosteroids, corticotropin and amphotericin B, also cause potassium loss and severe potassium depletion may occur when administered concurrently with furosemide.

Corticosteroids administered concurrently may cause sodium retention.
Concomitant administration of carbamazepine or aminoglutethimide may increase the risk of hyponatraemia.

Carbenoxolone, liquorice, B₂ sympathomimetics in large amounts, prolonged use of laxatives, reboxetine and amphotericin B may increase the risk of developing hypokalaemia.

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

A marked fall in blood pressure and deterioration in renal function may be seen when ACE inhibitors are added to furosemide therapy. The dose of furosemide should be reduced for at least three days, or the drug stopped, before initiating the ACE inhibitors or increasing the dose of an ACE inhibitor.

Certain non steroidal anti inflammatory agents (e.g. indometacin, acetylsalicylic acid) may attenuate the action of furosemide and may cause acute renal failure in cases of pre-existing hypovolaemia or dehydration. Salicylate toxicity may be increased by furosemide.

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.

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.

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).

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

Severe diuresis may occur if metolazone is administered concomitantly.

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.

4.6 PREGNANCY AND LACTATION

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

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

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

Furosemide leads to increased excretion of sodium and chloride and consequently water. In addition excretion of other electrolytes (in particular potassium, calcium and magnesium) is increased. Symptomatic electrolyte disturbances and metabolic alkalosis may develop in the form of a gradually increasing electrolyte deficit or, e.g. where higher furosemide doses are administered to patients with normal renal function, acute severe electrolyte losses.

Warning signs of electrolyte disturbances include increased thirst, headache, confusion, muscle cramps, tetany, muscle weakness, disorders of cardiac rhythm and gastrointestinal symptoms.

The diuretic action of furosemide may lead to or contribute to hypovolaemia and dehydration, especially in elderly patients. Severe fluid depletion may lead to haemoconcentration with a tendency for thromboses to develop.

Increased production of urine may provoke or aggravate complaints in patients with an obstruction of urinary outflow. Thus, acute retention of urine with possible secondary complications may occur, for example, in patients with bladder-emptying disorders, prostatic hyperplasia or narrowing of the urethra.

Furosemide may cause a reduction in 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.

Treatment with furosemide may lead to transitory increases in blood creatinine and urea levels and to an increase in cholesterol and triglyceride serum levels. Serum levels of uric acid may increase and attacks of gout may occur.

Glucose tolerance may decrease with furosemide. In patients with diabetes mellitus this may lead to a deterioration of metabolic control; latent diabetes mellitus may become manifest.

Gastrointestinal reactions such as nausea, vomiting or diarrhoea may occur. In isolated cases, intrahepatic cholestasis, an increase in liver transaminases or acute pancreatitis may develop.

Hearing disorders and tinnitus, although usually transitory, may occur in rare cases, particularly in patients with renal failure, hypoproteinaemia (e.g. in nephritic syndrome) and/or when intravenous furosemide has been given too rapidly.

The incidence of allergic reactions such as skin rash, photosensitivity, vasculitis, fever, interstitial nephritis or shock is very low but treatment should be withdrawn when these occur.

Skin and mucous membrane reactions may occasionally occur, e.g. itching, urticaria, other rashes or bullous lesions, erythema multiforme, exfoliative dermatitis, purpura.

Severe anaphylactic or anaphylactoid reactions (e.g. with shock) occur rarely.

Occasionally, thrombocytopenia may occur. In rare cases, leucopenia and eosinophilia may occur. In isolated cases, agranulocytosis, aplastic anaemia or haemolytic anaemia may develop.

Rarely, paraesthesiae may occur.

In premature infants furosemide may precipitate nephrocalcinosis/ nephrolithiasis. If furosemide is administered to premature infants during the first weeks of life, it may increase the risk of persistence of patent ductus arteriosus.

4.9 OVERDOSE

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 due to excessive diuresis. Symptoms of
these disturbances include severe hypotension (progressing to shock), acute renal failure, thrombosis, delirious states, flaccid paralysis, apathy and confusion.

Treatment should therefore be aimed at fluid replacement and correction of the electrolyte imbalance. 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.

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 designated to reduce absorption (e.g. activated charcoal).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES
CO3C A01 High Ceiling Diuretics, Sulphonamides, Plain.

Furosemide is one of the high ceiling diuretics, a term used to denote a group of diuretics that have a distinctive action on renal tubular function. The peak diuresis is far greater than that observed with other agents. The main site of action is the thick ascending loop of Henle where they inhibit electrolyte reabsorption. It increases renal blood flow without increasing the filtration rate. Such a change in renal haemodynamics reduces fluid and electrolyte reabsorption in the proximal tubule and may augment the initial diuretic response. Furosemide is an inhibitor of carbonic anhydrase but this activity is too weak to contribute to a proximal diuresis except when massive doses are employed. Furosemide enhances the excretion of both calcium and magnesium to an extent approximately proportional to the increase in sodium excretion. Unlike the thiazides, high ceiling diuretics do not increase calcium reabsorption in the distal tubule. The calcuiuric action of these agents is the basis for their use in symptomatic hypercalcaemia.

5.2 PHARMACOKINETIC PROPERTIES
Furosemide is incompletely but fairly rapidly absorbed from the gastrointestinal tract. Bioavailability is about 65%. It has a biphasic half-life in plasma with a terminal elimination phase up to about 2 hours but this is prolonged in neonates, and in patients with hepatic and renal insufficiency. It is extensively bound to plasma proteins but is rapidly secreted by the organic acid transport system of the proximal tubule. In this manner it gains access to the tubular fluid and eventually to its site of action more distally. It is mainly excreted in the urine largely unchanged, but also in the form of glucuronide and free amine metabolites. Variable amounts are also excreted in the bile. Furosemide crosses the placental barrier and is excreted in milk. Non renal elimination is considerably increased in renal failure. The clearance of furosemide is not increased by haemodialysis.
5.3 PRECLINICAL SAFETY DATA
Not relevant.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
Lactose Monohydrate
Magnesium Stearate (E572)
Sodium Starch Glycollate
Maize Starch

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
Tablet container: 3 years.
Blisters: 2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Containers: Do not store above 25°C. Keep the container tightly closed and store in the original container.

Blisters: Do not store above 25°C. Store in the original package. Keep blister in the outer carton.

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 and 1000 tablets

Blisters: (250 µm white opaque PVC and 20 µm hard temper aluminium foil).

Pack sizes: 28 and 56 tablets
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Not applicable.

7 MARKETING AUTHORISATION HOLDER
Co-pharma Limited
Unit 4, Metro Centre
Tolpits Lane
Watford
Hertfordshire
WD1 8SS

8 MARKETING AUTHORISATION NUMBER(S)
PL 13606/0116

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/08/2006

10 DATE OF REVISION OF THE TEXT
02/08/2006
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Furosemide 40 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 40mg Furosemide
For excipients, see 6.1

3 PHARMACEUTICAL FORM
Tablet.
Appearance: White, circular, flat bevelled edge tablet with a breakline on one side.

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
For oral use. The tablets should be swallowed with water.

Adults:

The usual initial daily dose is 40 mg. This may require adjustment until the effective dose is achieved. In mild cases 20 mg daily or 40 mg on alternate days may be sufficient, whereas in cases of resistant oedema daily doses of 80 mg and above may
be used as one or two doses daily, or intermittently. Severe cases may require gradual titration of the furosemide dosage up to 600mg.

In patients with chronic renal insufficiency, an initial daily dose of 250 mg is employed. If a satisfactory diuresis is not produced then the dose may be increased in steps of 250 mg 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 – 3 mg/kg body weight daily, up to a maximum total dose of 40 mg per day.

Elderly:

The usual adult dose, but caution is advised as furosemide is excreted more slowly in the elderly. Dosage should be titrated until the required response is achieved.

4.3 CONTRAINDICATIONS
Furosemide is contra-indicated in patients with hypovolaemia or dehydration, anuria or renal failure with anuria not responding to furosemide, renal failure as a result of poisoning by nephrotoxic or hepatotoxic agents or renal failure associated with hepatic coma, severe hypokalaemia, severe hyponatraemia, pre-comatose and comatose states associated with hepatic encephalopathy and breast feeding women.

Hypersensitivity to furosemide or any of the excipients. Patients allergic to sulphonamides may show cross-sensitivity to furosemide.

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Too vigorous diuresis may cause orthostatic hypotension or acute hypotensive episodes.

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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. Hypovolaemia or dehydration as well as any significant electrolyte and acid-base disturbances must be corrected. This may require temporary discontinuation of furosemide.
Urinary output must be secured. Patients with partial obstruction of urinary outflow, for example patients with prostatic hypertrophy or impairment of micturition, have an increased risk of developing acute retention and require careful monitoring.

Particularly careful monitoring is necessary in:

- Patients with hypotension.
- Patients who are at risk from a pronounced fall in blood pressure.
- Patients with latent or manifest diabetes. Furosemide may necessitate adjustment of control by hypoglycaemic agents in cases of diabetes mellitus.
- Patients with gout.
- Patients with hepatorenal syndrome.
- Patients with hypoproteinaemia, e.g. associated with nephritic syndrome (the effect of furosemide may be weakened and its ototoxicity potentiated). Cautious dose titration is required.
- Premature infants (possible development nephrocalcinosis/nephrolithiasis; renal function must be monitored and renal ultrasonography performed).

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 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

The concomitant administration of this preparation with cardiac glycosides or hypotensive agents may necessitate adjustment of the dosage of those drugs.

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

Impairment of renal function may develop in patients receiving treatment with furosemide and high doses of certain cephalosporins.

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.

Corticosteroids, corticotropin and amphotericin B, also cause potassium loss and severe potassium depletion may occur when administered concurrently with furosemide.

Corticosteroids administered concurrently may cause sodium retention.
Concomitant administration of carbamazepine or amnoglutethimide may increase the risk of hyponatraemia.

Carbenoxolone, liquorice, B₂ sympathomimetics in large amounts, prolonged use of laxatives, reboxetine and amphotericin B may increase the risk of developing hypokalaemia.

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

A marked fall in blood pressure and deterioration in renal function may be seen when ACE inhibitors are added to furosemide therapy. The dose of furosemide should be reduced for at least three days, or the drug stopped, before initiating the ACE inhibitors or increasing the dose of an ACE inhibitor.

Certain non steroidal anti inflammatory agents (e.g. indometacin, acetylsalicylic acid) may attenuate the action of furosemide and may cause acute renal failure in cases of pre-existing hypovolaemia or dehydration. Salicylate toxicity may be increased by furosemide.

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.

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.

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).

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

Severe diuresis may occur if metolazone is administered concomitantly.

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.

4.6 PREGNANCY AND LACTATION
Furosemide crosses the placental barrier. It must not be given during pregnancy unless there are compelling medical reasons. Treatment during pregnancy requires monitoring of foetal growth.

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

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
Furosemide leads to increased excretion of sodium and chloride and consequently water. In addition excretion of other electrolytes (in particular potassium, calcium and magnesium) is increased. Symptomatic electrolyte disturbances and metabolic alkalosis may develop in the form of a gradually increasing electrolyte deficit or, e.g. where higher furosemide doses are administered to patients with normal renal function, acute severe electrolyte losses.

Warning signs of electrolyte disturbances include increased thirst, headache, confusion, muscle cramps, tetany, muscle weakness, disorders of cardiac rhythm and gastrointestinal symptoms.

The diuretic action of furosemide may lead to or contribute to hypovolaemia and dehydration, especially in elderly patients. Severe fluid depletion may lead to haemoconcentration with a tendency for thromboses to develop.

Increased production of urine may provoke or aggravate complaints in patients with an obstruction of urinary outflow. Thus, acute retention of urine with possible secondary complications may occur, for example, in patients with bladder-emptying disorders, prostatic hyperplasia or narrowing of the urethra.

Furosemide may cause a reduction in 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.

Treatment with furosemide may lead to transitory increases in blood creatinine and urea levels and to an increase in cholesterol and triglyceride serum levels. Serum levels of uric acid may increase and attacks of gout may occur.

Glucose tolerance may decrease with furosemide. In patients with diabetes mellitus this may lead to a deterioration of metabolic control; latent diabetes mellitus may become manifest.

Gastrointestinal reactions such as nausea, vomiting or diarrhoea may occur. In isolated cases, intrahepatic cholestasis, an increase in liver transaminases or acute pancreatitis may develop.

Hearing disorders and tinnitus, although usually transitory, may occur in rare cases, particularly in patients with renal failure, hypoproteinaemia (e.g. in nephritic syndrome) and/or when intravenous furosemide has been given too rapidly.

The incidence of allergic reactions such as skin rash, photosensitivity, vasculitis, fever, interstitial nephritis or shock is very low but treatment should be withdrawn when these occur.

Skin and mucous membrane reactions may occasionally occur, e.g. itching, urticaria, other rashes or bullous lesions, erythema multiforme, exfoliative dermatitis, purpura.

Severe anaphylactic or anaphylactoid reactions (e.g. with shock) occur rarely.

Occasionally, thrombocytopenia may occur. In rare cases, leucopenia and eosinophilia may occur. In isolated cases, agranulocytosis, aplastic anaemia or haemolytic anaemia may develop.

Rarely, paraesthesiae may occur.

In premature infants furosemide may precipitate nephrocalcinosis/ nephrolithiasis. If furosemide is administered to premature infants during the first weeks of life, it may increase the risk of persistence of patent ductus arteriosus.

4.9 OVERDOSE

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 due to excessive diuresis. Symptoms of
these disturbances include severe hypotension (progressing to shock), acute renal failure, thrombosis, delirious states, flaccid paralysis, apathy and confusion.

Treatment should therefore be aimed at fluid replacement and correction of the electrolyte imbalance. 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.

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 designated to reduce absorption (e.g. activated charcoal).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Furosemide is one of the high ceiling diuretics, a term used to denote a group of diuretics that have a distinctive action on renal tubular function. The peak diuresis is far greater than that observed with other agents. The main site of action is the thick ascending loop of Henle where they inhibit electrolyte reabsorption. It increases renal blood flow without increasing the filtration rate. Such a change in renal haemodynamics reduces fluid and electrolyte re-absorption in the proximal tubule and may augment the initial diuretic response. Furosemide is an inhibitor of carbonic anhydrase but this activity is too weak to contribute to a proximal diuresis except when massive doses are employed. Furosemide enhances the excretion of both calcium and magnesium to an extent approximately proportional to the increase in sodium excretion. Unlike the thiazides, high ceiling diuretics do not increase calcium reabsorption in the distal tubule. The calciuic action of these agents is the basis for their use in symptomatic hypercalcaemia.

5.2 PHARMACOKINETIC PROPERTIES

Furosemide is incompletely but fairly rapidly absorbed from the gastrointestinal tract. Bioavailability is about 65%. It has a biphasic half-life in plasma with a terminal elimination phase up to about 2 hours but this is prolonged in neonates, and in patients with hepatic and renal insufficiency. It is extensively bound to plasma proteins but is rapidly secreted by the organic acid transport system of the proximal tubule. In this manner it gains access to the tubular fluid and eventually to its site of action more distally. It is mainly excreted in the urine largely unchanged, but also in the form of glucuronide and free amine metabolites. Variable amounts are also excreted in the bile. Furosemide crosses the placental barrier and is excreted in milk. Non renal elimination is considerably increased in renal failure. The clearance of furosemide is not increased by haemodialysis.
5.3 PRECLINICAL SAFETY DATA
Not relevant.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
Lactose Monohydrate
Magnesium Stearate (E572)
Sodium Starch Glycollate
Maize Starch

6.2 INCOMPATIBILITIES
None known.

6.3 SHELF LIFE
Tablet container: 3 years.
Blisters: 2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Containers: Do not store above 25°C. Keep the container tightly closed and store in the original container.

Blisters: Do not store above 25°C. Store in the original package. Keep blister in the outer carton.

6.5 NATURE AND CONTENTS OF CONTAINER
Tablet container and cap: (polypropylene container with low density polyethylene cap).

Pack sizes: 28, 100, 250, 500 and 1000 tablets

Blisters: (250 µm white opaque PVC and 20 µm hard temper aluminium foil).

Pack sizes: 28 tablets
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Not applicable.

7 MARKETING AUTHORISATION HOLDER
Co-pharma Limited
Unit 4, Metro Centre
Tolpits Lane
Watford
Hertfordshire
WD1 8SS

8 MARKETING AUTHORISATION NUMBER(S)
PL 13606/0117

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION
02/08/2006

10 DATE OF REVISION OF THE TEXT
02/08/2006
Please read all of this leaflet carefully before you start taking this medicine. Keep the leaflet, you may need to read it again.

This medicine has been prescribed for you personally. Do not pass it on to others. It may harm others even if their symptoms are the same as yours. If you have any further questions, please ask your doctor or pharmacist.

The name of this medicine is:

**FUROSEMIDE 20 MG TABLETS OR FUROSEMIDE 40 MG TABLETS**

The tablets are available in two strengths and contain either 20 mg or 40 mg of the active substance furosemide. Other ingredients are lactose monohydrate, magnesium stearate, sodium starch glycolate and maize starch.

**Product Licence holder** is Co-pharma Ltd., Unit 4, Metro Centre, Tolpits Lane, Watford, Herts, WD1 9SS. The tablets are manufactured by Clonmel Healthcare Ltd, Waterford Road, Clonmel, Co. Tipperary, Ireland.

**What the tablets are and what they are used for**

The tablets are white circular tablets with a breakline on one side. Furosemide belongs to a group of drugs called diuretics (also called water tablets). It works by increasing the volume of urine produced by the kidneys, helping to remove excess fluids from the body.

The tablets are supplied to your pharmacist in packs containing 28, 56, 100, 250, 500 and 1000 tablets for Furosemide 20mg tablets and in packs containing 28, 100, 250, 500 and 1000 tablets for Furosemide 40mg tablets, who will then provide you with the required number of tablets as prescribed by your doctor (not all pack sizes may be marketed).

Furosemide is used to treat oedema (fluid retention) caused by heart failure, certain liver and kidney disorders or high blood pressure. It is also used to manage a condition called oliguria, where the body produces an abnormally small amount of urine, due to kidney disease.

**Before you take Furosemide Tablets**

**Do not take if:**

- You are allergic to furosemide, any of the other ingredients or sulphonamides (e.g. sulfamethoxazole).
- You are producing no urine or very little urine.
- You have liver disease or kidney failure.
- You have low levels of potassium or sodium in your blood.
- You have low circulating blood volume or you are dehydrated.
- You are pregnant or breast feeding.

**Take special care and make sure your doctor is aware if:**

- You have hypotension (low blood pressure) or hypoproteinaemia (low levels of protein in the blood).
- You have liver or kidney impairment.
- You have diabetes.
- You have an enlarged prostate gland.
- You have difficulty urinating.
- You have a history of gout.

If you are elderly you may be more sensitive to the effects of furosemide tablets. If this medicine is to be given to a premature infant, your doctor should monitor the child's kidney function.

This medicine may affect blood potassium, sodium and creatinine levels. Your doctor may monitor these by means of blood tests, especially if you are at risk of developing electrolyte imbalances (abnormal salt levels in the blood) or if you have significant additional fluid loss.

**Check with your doctor before taking Furosemide Tablets if you are taking any other medicines, including any not prescribed by your doctor, particularly any of the following:**

- Medicines used to treat high blood pressure (e.g. metolazone).
- Medicines to raise blood pressure (e.g. amlopril, nicorandil).
- Antibiotics (e.g. cefotaxime, neomycin).
- You are taking a type of medicine called an ACE inhibitor (e.g. captopril).
- Non-steroidal anti-inflammatory drugs (e.g. ibuprofen).
- Salicylates (e.g. aspirin).
- Medicines to treat heart failure (e.g. digoxin).
- Medicines used to treat a heart condition (e.g. digoxin).
- Corticosteroids (e.g. prednisolone).
- Medicines used for diabetes.
- Muscle relaxant drugs used for anaesthesia during surgery.
- Laxatives.
- Reboxetine or lithium (used to treat depression), corticosteroids (to treat adrenocortical function), amphotericin B (used to treat fungal infections), carbamazepine or phenytoin (used to control epilepsy), antiseptic or disinfectant (used to treat cancer), carbamazepine or quinidine (used to treat mouth ulcers), metoclopramide (a diuretic), probenecid (used to control gout), methotrexate (to treat rheumatoid arthritis), theophylline (used to help your breathing) or sucralfate (to treat gastro-duodenal ulcers).

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine as it contains lactose.

This medicine may reduce mental alertness and cause dizziness and blurred vision. Do not drive or operate machinery if it has this effect on you.
How to take

For oral use. The tablets should be taken in the morning unless instructed otherwise by your doctor and be swallowed with a drink of water. You should take your tablets as directed by your doctor. The pharmacist's label should tell you how much to take and how often. If it does not or you are not sure ask your doctor or pharmacist.

Adults: The usual initial daily dose is 40 mg. This may require adjustment until the effective dose is achieved. In mild cases 20 mg daily or 40 mg on alternate days may be sufficient.

If you suffer from chronic kidney trouble, your doctor may prescribe a starting dose of 250 mg every 4 to 6 hourly up to a maximum of 1500 mg per day. If you are elderly you may be given a lower dose to start.

Children:

If Furosemide tablets are prescribed for a child make sure that the tablets are taken as instructed by a doctor. The dosage is worked out depending on the child's weight. The usual dose is 1 - 3 mg for each kilogram of the child's body weight. Do not exceed 40 mg per day.

If you take more tablets than you should:

If you have taken more tablets than you should contact your nearest hospital casualty department or doctor immediately.

If you forget to take a dose of Furosemide Tablets:

Take the missed dose as soon as you remember, unless it is evening, in which case if you do take the missed dose you may need to get up in the night to pass water. Take your next dose at the usual time. Do not take a double dose to make up for the missed dose.

Possible side effects:

Like all medicines, furosemide may sometimes cause side-effects. If you experience any of the following stop taking the tablets and contact your doctor or hospital casualty department immediately:

- An allergic reaction e.g. skin rash, itching, swelling.
- Changes in fluid and salt levels in the body. Symptoms may include thirst, headache, confusion, muscle cramps, spasm or weakness, change in heart beat or stomach upset.
- Low blood pressure. Symptoms may include difficulty in concentration and reaction times may be affected, light-headedness, sensations of pressure in the head, headache, dizziness, drowsiness, weakness, vision disorders, dry mouth. Low blood pressure may occur when standing up after sitting or lying down.
- A rise in creatinine or urea levels in the body.
- An increased level of uric acid in the blood which may cause gout.
- Diabetes or if you already have diabetes you may need to increase your insulin dose.
- Nausea, vomiting, diarrhoea.
- Changes in your cholesterol or triglyceride levels.
- Nephrolcalcinosis in premature infants (a condition where deposits of calcium form in the kidneys).

The diuretic action of furosemide may cause dehydration and low blood volume, especially if you are elderly. Severe fluid loss may lead to an increase in red blood cells which may result in thrombosis developing. If you already have a problem passing water your condition may be aggravated.

The following other unwanted effects may occur:

- Blood disorders. (Symptoms include fever, tiredness, bruising and sometimes abnormal bleeding).
- Kidney or liver disorders.
- Pancreatitis (symptoms may include severe abdominal pain moving to the back, fever, loss of appetite, nausea and vomiting).
- Hearing difficulty or ringing in the ears.
- Pins and needles.

If you experience any of the above or are concerned about anything or you notice anything unusual contact your doctor or pharmacist.

Storing the tablets

Keep out of the reach and sight of children.
Blisters: Do not store above 25°C. Store in the original package. Keep blister in the outer carton.
Tablet container: Do not store above 25°C. Keep the container tightly closed. Store in the original container.

Do not use the tablets after the expiry date shown on the label.

If you have any tablets remaining after your doctor tells you to stop taking them, return them to your pharmacist for safe disposal.

This leaflet was prepared June 2006
UKPAR Furosemide 20mg and 40mg Tablets Co-Pharma Ltd
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- You have diabetes.
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- You have difficulty urinating.
- You have a history of gout.

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- Medicines to raise blood pressure (e.g. clonidine, norepinephrine).
- Antibiotics (e.g. cephalaxin, neomycin).
- You are taking a type of medicine called an ACE inhibitor (e.g. captopril).
- Non-steroidal anti-inflammatory drugs (e.g. indomethacin).
- Salicylates (e.g. aspirin).
- Medicines to treat heart failure (e.g. digoxin).
- Medicines used to treat a heart condition (e.g. digoxin).
- Corticosteroids (e.g. prednisolone).
- Medicines used for diabetes.
- Muscle relaxant drugs used for anaesthesia during surgery.
- Laxatives.
- Reboxetine or lithium (used to treat depression), corticosteroids (to treat asthma/asthma-like symptoms), amphotericin B (used to treat fungal infections), carbamazepine or phenytoin (used to control epilepsy), ammonium chloride or osmotic (used to treat cancer), carbamazepine or leucine (used to treat mouth ulcers), metolazone (diuretic), probenecid (used to control gout), methotrexate (to treat rheumatoid arthritis), morphine (used to help your breathing) or sacrist (to treat gastrointestinal ulcers).

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This leaflet was prepared June 2006
Each tablet contains Furosemide 40 mg. Also includes lactose (see leaflet for further information).

Tablets for oral use. To be taken as directed by a physician.

Please read the leaflet provided carefully before use.

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Do not store above 25°C. Keep the container tightly closed and store in the original container.

PL Holder: Co-pharma Limited, Watford, Herts, UK, WD1 8SS.

PL 13606/0016-17

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