FUROSEMIDE 10 MG/ML SOLUTION FOR INJECTION OR INFUSION
PL 20851/0003 AND PL 20851/0004

UKPAR

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FUROSEMIDE 10 MG/ML SOLUTION FOR INJECTION OR INFUSION
PL 20851/0003 AND PL 20851/0004

LAY SUMMARY

The MHRA has granted Wockhardt UK Limited Marketing Authorisations (licences) for the medicinal products Furosemide 10mg/ml Solution for Injection or Infusion (PL 20851/0003 and PL 20851/0004). These prescription only medicines (POM) are medicines used to remove excess water from the body. They are used in conditions such as those which affect the heart, lungs, kidneys, liver, blood vessels or blood pressure which may lead to a build up of water in the body.

These medicines contain the active ingredient furosemide, which helps the kidneys get rid of water that is not needed in the body.

No new or unexpected safety concerns arose from these applications. It was therefore judged that the benefits of taking this medicine outweigh the risks and Marketing Authorisations have been granted.

These licences were subsequently cancelled on 11th April 2007.
Furosemide 10mg/ml Solution for Injection or Infusion
PL 20851/0003 AND PL 20851/0004

Scientific Discussion

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Furosemide 10mg/ml Solution for injection or Infusion (PL 20851/0003 and PL 20851/0004) to Wockhardt UK Limited on 12th July 2006. The products are prescription only medicines.

The applications were submitted as abridged applications according to article 10.1 [formerly article 10.1(a)(iii)] of Directive 2001/83/EC, claiming essential similarity to the original product Lasix 10mg/ml Solution for Injection (Hoechst Marion Roussel Ltd), which has been marketed in the UK for more than 10 years.

The products contain the active ingredient furosemide and are indicated in all conditions requiring prompt diuresis including cardiac, pulmonary, hepatic and renal oedema and peripheral oedema.

Furosemide is a loop diuretic which inhibits sodium and chloride reabsorption at the Loop of Henle.

These applications for Furosemide 10mg/ml Solution for Injection or Infusion in 2ml ampoules and 25ml vials were submitted at the same time and were assessed simultaneously. Consequently, all sections of this Scientific Discussion refer to both products.

These licences were subsequently cancelled on 11th April 2007.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Furosemide
Recommended International Nonpropriety Name (INN): Furosemide
Compendial Name: Furosemide
Chemical Names:
5-(aminosulfonyl)-4-chloro-2-[(2-furanylmethyl)amino]benzoic acid;
4-chloro-N-furfuryl-5-sulfamoylanthranilic acid;
Structure:

Molecular formula: C_{12}H_{11}ClN_{2}O_{5}
Molecular weight: 330.7
General properties: A white or almost white, crystalline powder, practically insoluble in water, soluble in acetone, sparingly soluble in alcohol, practically insoluble in methylene chloride. It dissolves in dilute solutions of alkali hydroxides.

Furosemide is the subject of a European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance furosemide. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided and comply with the proposed specification.

The finished product is packed in plastic drums lined with two polyethylene bags (one transparent and one black). Specifications have been provided for all packaging used. All primary packaging complies with current European Directives concerning contact with food.

Based on stability studies, a retest period of 5 years has been proposed for the active substance. Suitable post approval stability commitments have been given to provide additional stability data as and when it becomes available.
DRUG PRODUCT

Other ingredients
Other ingredients consist of pharmaceutical excipients, namely sodium chloride, sodium hydroxide and water for injections. All excipients used comply with their respective Ph Eur monograph. Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contain materials of animal or human origin.

Product development
The applicant has provided a suitable product development section.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of each strength of product. The results appear satisfactory.

Finished product specification
The finished product specification is satisfactory. Test methods have been described and have been adequately validated as appropriate. Batch data have been provided and comply with the release specification. Certificate of analysis have been provided for all working standards used.

Container Closure System
The finished product is packaged in either a 2ml ampoule (PL 20851/0003) or a 25ml vial (PL 20851/0004). Both the ampoule and vial are type I topaz glass, the vial also has a bromobutyl stopper (type I) and aluminium and polypropylene flip-off cap.

The finished product is packaged into 1, 5 and 10 ampoule packs. Not all pack sizes are to be marketed and the applicant has confirmed that they will submit the packaging for approval before marketing any pack size.

Specifications and Certificates of Analysis for all packaging have been provided. These are satisfactory. The primary packaging has been shown to comply with relevant regulations regarding suitability for use with parenteral solutions.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, with the storage instructions “Store in the original packaging”.

The applicant has provided suitable post approval stability commitments to follow-up the current batches on stability and to add the first three commercial batches as they become available.
Bioequivalence
No bioequivalence studies have been performed and none are required for injectable solutions. Bioequivalence with the reference product has been shown through the quantitative and qualitative composition of the products.

ADMINISTRATIVE
Expert Report
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics (SPC)
These are consistent with those for the reference products and are satisfactory.

Labelling
These are satisfactory

Patient Information Leaflet
These are consistent with the SPC and are satisfactory. The marketing authorisation holder has provided a commitment to update the marketing authorisation no later than 1st July 2008 with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups.

MAA Forms
These are satisfactory.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.
**PRECLINICAL ASSESSMENT**

No new preclinical data have been supplied with these applications and none are required for applications of this type.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
The pharmacology of furosemide is well-established. No clinical pharmacology data is required for these generic injection solutions.

EFFICACY
The efficacy of furosemide is well-established. No new efficacy data is required for these generic applications.

SAFETY
The safety of furosemide is well-established. No new safety data is required for these generic applications.

EXPERT REPORT
The Clinical Expert Report has been written by a suitably qualified physician and is a suitable summary of the clinical aspects of the dossier.

SUMMARY OF PRODUCT CHARACTERISTICS
These are consistent with those for the reference products and are satisfactory.

PATIENT INFORMATION LEAFLET
These are consistent with the SPC and are satisfactory.

LABELLING
These are satisfactory.

MAA FORM
These are satisfactory

RECOMMENDATION
The grant of a marketing authorisation is recommended.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Furosemide 10mg/ml Solution for Injection or Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

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

EFFICACY
Furosemide is a well-known drug and has been used as a diuretic for many years. The applicant has demonstrated essential similarity to the innovator product, Lasix 10mg/ml Liquid.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s products and the innovator products are interchangeable. 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 FOR ASSESSMENT**

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<td>1</td>
<td>The MHRA received the marketing authorisation applications on 23/12/2004.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 07/02/2005.</td>
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<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the dossier on 14/07/2005 and again on 07/04/2006.</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 15/12/2005 and 22/05/2006.</td>
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<td>The applications were determined on 12/07/2006.</td>
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## STEPS TAKEN AFTER ASSESSMENT

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<td>11-04-2007</td>
<td>Cancellation</td>
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<td>Approved 11-04-2007</td>
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FUROSEMIDE 10 MG/ML SOLUTION FOR INJECTION OR INFUSION
PL 20851/0003

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Furosemide 10mg/ml Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml contains 10mg of furosemide.

Each 2ml ampoule contains 20mg of furosemide.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Solution for injection or infusion

The solution is colourless or almost colourless.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Furosemide 10mg/ml Injection is a diuretic indicated for use when a prompt and effective diuresis is required. The intravenous formulation is appropriate for use in emergencies or when oral therapy is precluded. Indications include cardiac, pulmonary, hepatic and renal oedema.

4.2 Posology and method of administration
Route of administration: intramuscular or intravenous use.

Adults
Intravenous furosemide must be injected or infused slowly; a rate of 4 mg per minute must not be exceeded. In patients with severe impairment of renal function (serum creatinine>5 mg/dl), it is recommended that an infusion rate of 2.5 mg per minute is not exceeded.

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

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

Doses of 20 to 50 mg intramuscularly or intravenously may be given initially. If larger doses are required, they should be given by 20 mg increments and not given more often than every two hours. If doses greater than 50 mg are required it is recommended that they be given by slow intravenous infusion. The recommended maximum daily dose of furosemide administration is 1,500 mg.

Elderly: The dosage recommendations for adults apply, but in the elderly furosemide is generally eliminated more slowly. Dosage should be titrated until the required response is achieved.
Children: Parenteral doses for children range from 0.5 to 1.5 mg/kg body weight daily up to a maximum total daily dose of 20 mg.

4.3 Contraindications
Furosemide 10mg/ml Injection 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 of Furosemide 10mg/ml Injection. Patients allergic to sulphonamides may show cross-sensitivity to furosemide.

4.4 Special warnings and precautions for use
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.

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

Particularly careful monitoring is necessary in:
- patients with hypotension
- patients who are at risk from a pronounced fall in blood pressure
- patients where latent diabetes may become manifest or the insulin requirements of diabetic patients may increase
- patients with gout
- patients with hepatorenal syndrome
- patients with hypoproteinaemia, e.g. associated with nephrotic syndrome (the effect of furosemide may be weakened and its ototoxicity potentiated). Cautious dose titration is required
- premature infants (possible development of nephrocalcinosis/nephrolithiasis; renal function must be monitored and renal ultrasonography performed)

Caution should be observed in patients liable to electrolyte deficiency. 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.

This medicinal product contains 0.26mol of sodium in a 2ml ampoule. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction
The dosage of concurrently administered cardiac glycosides or anti-hypertensive agents may require adjustment. 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 inhibitor or increasing the dose of an ACE inhibitor.

The toxic effects of nephrotoxic antibiotics may be increased by concomitant administration of potent diuretics such as furosemide.

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

In common with other diuretics, serum lithium levels may be increased when lithium is given concomitantly with furosemide, resulting in increased lithium toxicity. Therefore, it is
recommended that lithium levels are carefully monitored and where necessary the lithium dosage is adjusted in patients receiving this combination.

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 sometimes attenuate the effects of other drugs (e.g. the effects of anti-diabetics and of pressor amines) and sometimes potentiate them (e.g. the effects of salicylates, theophylline and curare-type muscle relaxants).

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.

Concomitant administration of carbamazepine or aminoglutethimide may increase the risk of hyponatraemia.

Corticosteroids administered concurrently may cause sodium retention.

Corticosteroids, carbenoxolone, liquorice, β2-sympathomimetics in large amounts, prolonged use of laxatives, reboxetine and amphotericin may increase the risk of developing hypokalaemia.

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.

4.6 Pregnancy and lactation
Results of animal work, in general, show no hazardous effect of furosemide in pregnancy. There is clinical evidence of safety of the drug in the third trimester of human pregnancy; however, 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 may impair ability to drive or operate dangerous machinery.

4.8 Undesirable effects
Furosemide 10mg/ml Injection is generally well tolerated.

Eosinophilia is rare.

Occasionally, thrombocytopenia may occur. In rare cases, leucopenia and, in isolated cases, agranulocytosis, aplastic anaemia or haemolytic anaemia may develop.
Bone marrow depression has been reported as a rare complication and necessitates withdrawal of treatment.

Rarely, paraesthesiae may occur.

Serum calcium levels may be reduced; in very rare cases tetany has been observed.

Nephrocalcinosis / Nephrolithiasis has been reported in premature infants.

Serum cholesterol and triglyceride levels may rise during furosemide treatment. During long term therapy they will usually return to normal within six months.

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.

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

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.

In isolated cases, intrahepatic cholestasis, an increase in liver transaminases or acute pancreatitis may develop.

The incidence of allergic reactions, such as skin rashes, photosensitivity, vasculitis, fever, interstitial nephritis or shock is very low, but when these occur treatment should be withdrawn. Skin and mucous membrane reactions may occasionally occur, e.g. itching, urticaria, other rashes or bullous lesions, erythema multiforme, exfoliative dermatitis, purpura.

As with other diuretics, electrolytes and water balance may be disturbed as a result of diuresis after prolonged therapy. 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, hypotension, confusion, muscle cramps, tetany, muscle weakness, disorders of cardiac rhythm and gastrointestinal symptoms. Pre-existing metabolic alkalosis (e.g. in decompensated cirrhosis of the liver) may be aggravated by furosemide treatment.

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.

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

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

Side-effects of a minor nature such as nausea, malaise or gastric upset (vomiting or diarrhoea) may occur but are not usually severe enough to necessitate withdrawal of treatment.
As with other diuretics, treatment with furosemide may lead to transitory increases in blood creatinine and urea levels. Serum levels of uric acid may increase and attacks of gout may occur.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
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 Henle 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 applicable.
6  PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium chloride
Sodium hydroxide
Water for injections

6.2 Incompatibilities
Furosemide may precipitate out of solution in fluids of low pH (e.g. dextrose solutions).

6.3 Shelf life
Three years

6.4 Special precautions for storage
Store in the original package

6.5 Nature and contents of container
Type I amber coloured glass ampoule of 3ml capacity. Each pack contains 1, 5 or 10 ampoules.*

*Not all pack sizes may be marketed

6.6 Special precautions for disposal
From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately.

For single use only.

Furosemide 10mg/ml Injection solution should not be mixed with any other drugs in the injection bottle.

Intravenous furosemide must be injected or infused slowly; a rate of 4 mg per minute must not be exceeded. In patients with severe impairment of renal function (serum creatinine>5 mg/dl), it is recommended that an infusion rate of 2.5 mg per minute is not exceeded.

7  MARKETING AUTHORISATION HOLDER
Wockhardt UK Limited
Ash Road North
Wrexham
LL13 9UF
UK

8  MARKETING AUTHORISATION NUMBER(S)
PL 20851/0003

9  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
12/07/2006

10 DATE OF REVISION OF THE TEXT
12/07/2006
Furosemide 10mg/ml Solution for Injection or Infusion

1 NAME OF THE MEDICINAL PRODUCT
Furosemide 10mg/ml Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml contains 10mg of furosemide. Each 25ml vial contains 250mg of furosemide.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Solution for injection or infusion

The solution is colourless or almost colourless.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Furosemide 10mg/ml Injection is a diuretic indicated for use when a prompt and effective diuresis is required. The intravenous formulation is appropriate for use in emergencies or when oral therapy is precluded. Indications include cardiac, pulmonary, hepatic and renal oedema.

4.2 Posology and method of administration
Route of administration: intramuscular or intravenous use.

Adults
Intravenous furosemide must be injected or infused slowly; a rate of 4 mg per minute must not be exceeded. In patients with severe impairment of renal function (serum creatinine>5 mg/dl), it is recommended that an infusion rate of 2.5 mg per minute is not exceeded.

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

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

Doses of 20 to 50 mg intramuscularly or intravenously may be given initially. If larger doses are required, they should be given by 20 mg increments and not given more often than every two hours. If doses greater than 50 mg are required it is recommended that they be given by slow intravenous infusion. The recommended maximum daily dose of furosemide administration is 1,500 mg.

Elderly: The dosage recommendations for adults apply, but in the elderly furosemide is generally eliminated more slowly. Dosage should be titrated until the required response is achieved.

Children: Parenteral doses for children range from 0.5 to 1.5 mg/kg body weight daily up to a maximum total daily dose of 20 mg.

4.3 Contraindications
Furosemide 10mg/ml Injection 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 of Furosemide 10mg/ml Injection. Patients allergic to sulphonamides may show cross-sensitivity to furosemide.

4.4 Special warnings and precautions for use

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.

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

Particularly careful monitoring is necessary in:

- patients with hypotension
- patients who are at risk from a pronounced fall in blood pressure
- patients where latent diabetes may become manifest or the insulin requirements of diabetic patients may increase
- patients with gout
- patients with hepatorenal syndrome
- patients with hypoproteinaemia, e.g., associated with nephrotic syndrome (the effect of furosemide may be weakened and its ototoxicity potentiated). Cautious dose titration is required
- premature infants (possible development of nephrocalcinosis/nephrolithiasis; renal function must be monitored and renal ultrasonography performed)

Caution should be observed in patients liable to electrolyte deficiency. 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.

This medicinal product contains 0.26mol of sodium in a 2mlampoule. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

The dosage of concurrently administered cardiac glycosides or anti-hypertensive agents may require adjustment. 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 inhibitor or increasing the dose of an ACE inhibitor.

The toxic effects of nephrotoxic antibiotics may be increased by concomitant administration of potent diuretics such as furosemide.

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

In common with other diuretics, serum lithium levels may be increased when lithium is given concomitantly with furosemide, resulting in increased lithium toxicity. Therefore, it is recommended that lithium levels are carefully monitored and where necessary the lithium dosage is adjusted in patients receiving this combination.

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 sometimes attenuate the effects of other drugs (e.g. the effects of anti-diabetics and of pressor amines) and sometimes potentiate them (e.g. the effects of salicylates, theophylline and curare-type muscle relaxants).

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.

Concomitant administration of carbamazepine or aminoglutethimide may increase the risk of hyponatraemia.

Corticosteroids administered concurrently may cause sodium retention.

Corticosteroids, carbenoxolone, liquorice, β₂-sympathomimetics in large amounts, prolonged use of laxatives, reboxetine and amphotericin may increase the risk of developing hypokalaemia.

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.

### 4.6 Pregnancy and lactation

Results of animal work, in general, show no hazardous effect of furosemide in pregnancy. There is clinical evidence of safety of the drug in the third trimester of human pregnancy; however, 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 may impair ability to drive or operate dangerous machinery.

### 4.8 Undesirable effects

Furosemide 10mg/ml Injection is generally well tolerated.

Eosinophilia is rare.

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

Bone marrow depression has been reported as a rare complication and necessitates withdrawal of treatment.

Rarely, paraesthesiae may occur.
Serum calcium levels may be reduced; in very rare cases tetany has been observed.

Nephrocalcinosis / Nephrolithiasis has been reported in premature infants.

Serum cholesterol and triglyceride levels may rise during furosemide treatment. During long term therapy they will usually return to normal within six months.

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.

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

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.

In isolated cases, intrahepatic cholestasis, an increase in liver transaminases or acute pancreatitis may develop.

The incidence of allergic reactions, such as skin rashes, photosensitivity, vasculitis, fever, interstitial nephritis or shock is very low, but when these occur treatment should be withdrawn. Skin and mucous membrane reactions may occasionally occur, e.g. itching, urticaria, other rashes or bullous lesions, erythema multiforme, exfoliative dermatitis, purpura.

As with other diuretics, electrolytes and water balance may be disturbed as a result of diuresis after prolonged therapy. 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, hypotension, confusion, muscle cramps, tetany, muscle weakness, disorders of cardiac rhythm and gastrointestinal symptoms. Pre-existing metabolic alkalosis (e.g. in decompensated cirrhosis of the liver) may be aggravated by furosemide treatment.

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.

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

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

Side-effects of a minor nature such as nausea, malaise or gastric upset (vomiting or diarrhoea) may occur but are not usually severe enough to necessitate withdrawal of treatment.

As with other diuretics, treatment with furosemide may lead to transitory increases in blood creatinine and urea levels. Serum levels of uric acid may increase and attacks of gout may occur.
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 designed to reduce absorption (e.g. activated charcoal).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 Henle 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 applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide
Water for injections
6.2 Incompatibilities
Furosemide may precipitate out of solution in fluids of low pH (e.g. dextrose solutions).

6.3 Shelf life
Three years

6.4 Special precautions for storage
Store in the original package

6.5 Nature and contents of container
Type I amber coloured glass vial (25ml capacity) sealed with a bromobutyl stopper, aluminium overseal and polypropylene flip-off cap. Each pack contains 1, 5 or 10 ampoules*.

*Not all pack sizes may be marketed

6.6 Special precautions for disposal
From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately.

For single use only.

Furosemide 10mg/ml Injection solution should not be mixed with any other drugs in the injection bottle.

Intravenous furosemide must be injected or infused slowly; a rate of 4 mg per minute must not be exceeded. In patients with severe impairment of renal function (serum creatinine>5 mg/dl), it is recommended that an infusion rate of 2.5 mg per minute is not exceeded.

7 MARKETING AUTHORISATION HOLDER
Wockhardt UK Limited
Ash Road North
Wrexham
LL13 9UF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 20851/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
12/07/2006

10 DATE OF REVISION OF THE TEXT
12/07/2006
FUROSEMIDE 10 MG/ML SOLUTION FOR INJECTION OR INFUSION
PL 20851/0003 AND PL 20851/0004

PRODUCT INFORMATION LEAFLET

PACKAGE LEAFLET
FUROSEMIDE 10MG/ML SOLUTION FOR INJECTION OR INFUSION
Furosemide solution for injection or infusion

The active ingredient in this medicine is furosemide. This is the new name for Lasix. The ingredient itself has not changed.

Read all of this leaflet carefully before you are given this medicine. Keep this leaflet. You may need to read it again.
If you have further questions, please ask your doctor or nurse.

In this leaflet:
1. What is Furosemide 10mg/ml Solution for Injection or Infusion and what is it used for?
2. Before you are given Furosemide 10mg/ml Solution for Injection or Infusion
3. How Furosemide 10mg/ml Solution for Injection or Infusion will be given to you
4. Possible side effects
5. Storing Furosemide 10mg/ml Solution for Injection or Infusion

The active substance in the injection is furosemide.

The other ingredients are sodium chloride, sodium hydroxide and water for injections.

Furosemide 10mg/ml Solution for Injection or Infusion is manufactured by Laboratori Reig Jofré, S.A. deJarana, s/n, (Polígono Industrial) 46207 Toledo, Spain for the Marketing Authorisation holder Woolworth UK Limited, Ash Road North, Wrexham LL13 9UF.

WHAT IS FUROSEMIDE 10MG/ML SOLUTION FOR INJECTION OR INFUSION AND WHAT IS IT USED FOR?

Furosemide 10mg/ml Solution for Injection or Infusion is a colourless or almost colourless solution for injection or infusion.
It is available in two presentations: a 2ml amber glass ampoule containing 20mg of furosemide and a 25ml amber glass vial containing 250mg of furosemide. Both presentations are available in single packs.

Furosemide belongs to a group of medicines called loop diuretics which are used to get rid of excess fluid from the body.

Furosemide injection is used to get rid of excess fluid from the body, which has accumulated due to problems with the heart, lungs, liver or kidneys. It is used in emergency situations or in situations when you are unable to take medicines by mouth.

2. BEFORE YOU ARE GIVEN FUROSEMIDE 10MG/ML SOLUTION FOR INJECTION OR INFUSION

You will not be given furosemide injection if:

- You have been told you are allergic to furosemide or any of the other ingredients in the injection. Check by reading the list of ingredients above.
- You have been told you are allergic to certain antibiotics, called sulphonamides.
- You are suffering from dehydration or have lost a lot of blood.
- You have kidney failure caused by certain drugs.
- You have reduced consciousness due to liver disease.
- You have stopped producing urine (water) in spite of treatment with furosemide.
- You have very low levels of potassium or sodium in your blood.

Consult your doctor if any of the above warnings applies to you or has applied to you in the past.

Your doctor will take special care when giving you furosemide injection if:

- You have problems with your prostate gland or difficulty in passing water.
- You have, or are liable to, very low blood pressure.
- You have diabetes mellitus or gout.
- You have liver or kidney problems.
- You have low levels of protein in your blood.
- You are liable to low levels of salts in your blood – you may need blood tests to check these.

Caes are required in premature babies.

Pregnancy

Furosemide injection should not be given to you if you are pregnant unless your doctor considers it essential. You should let your doctor know if you think you may be pregnant or are trying for a baby.

Breast-feeding

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Women who are breast feeding should not be given furosemide. If you are breast feeding you should discuss this with your doctor before being given furosemide.

Driving and using machines:

Furosemide can affect your ability to drive or use machines. If you are affected, do not drive or operate machinery.

Important information about some of the ingredients of furosemide injection:

Each 2ml ampoule contains 3.28mol of sodium and each 25ml vial contains 3.25mol of sodium. This should be taken into consideration if you are on a controlled sodium diet.

Taking other medicines

Taking another medicine while you are being given furosemide injection can affect how it or the other medicine works. Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those you may have bought yourself without a prescription. Please check with your doctor if you are taking any of the following (or any other medication):

- Other drugs taken for high blood pressure, especially ACE inhibitors such as captopril, but also alpha-blockers, beta-blockers and calcium channel blockers.
- Certain antibiotics including some cephalosporins, aminoglycosides (examples include amikacin, gentamicin, netilmicin) and vancomycin.
- Lithium, and certain other drugs taken for mental problems, such as reboxetine, pimozide and serindole.
- Drugs used to reduce inflammation (NSAIDs) such as aspirin, ibuprofen, indomethacin and ketorolac.
- Drugs used for diabetes such as glibenclamide.
- Dopamine and similar drugs, used to increase blood pressure.
- Certain drugs used to treat asthma, including theophylline and beta-agonists such as salbutamol.
- Muscle relaxant drugs, such as atracurium, vecuronium and tizanidine.
- Some medicines used for heart problems including sotalol, disopyramide, flecainide, quinidine, lidocaine, mexiletine, digoxin, digoxin and amiodarone.
- Cisplatin and amphotericin B, used in cancer therapy.
- Carbamazepine and phenytoin which are taken for epilepsy.
- Steroids such as cortisone and hydrocortisone.
- Carbamazepine and phenytoin, used to treat stomach ulcers.
- Laxatives.
- Amphotericin B, used to treat fungal infections.
- Probenecid, a drug used for the prevention of gout.
- Methotrexate, a drug used for cancer treatment or arthritis.
- Terfenadine, taken for allergies.

3. HOW WILL FUROSEMIDE 10MG/ML SOLUTION FOR INJECTION OR INFUSION BE GIVEN TO YOU

Your injection will be given to you by a doctor or nurse. The solution can be injected directly into a muscle (intramuscularly), be given by a slow injection into a vein (intravenously) over several minutes or diluted with another fluid and given by a drip over a longer period of time.

In adults and the elderly, the usual dose is 20 to 60mg, increasing by 20mg every two hours if necessary. The maximum daily dose should not be more than 1,500mg.

In children the dose will range from 0.6 to 1.5mg/kg of bodyweight daily. The maximum daily dose should not be more than 20mg.

Your doctor will decide the dose which is best for you. If you do not understand, or are in any doubt, ask your doctor or nurse.

4. POSSIBLE SIDE EFFECTS

Like any other medication, furosemide can cause side effects. The most common side-effects that some other patients have had (as well as the expected effect of passing a lot of water) are low blood pressure and a low body level of salts such as sodium, potassium or calcium (symptoms of these include dry mouth, thirst, weakness, confusion, drowsiness, headache, weakness, muscle cramps or spasms, and irregular heart beat).

Other side-effects that have been reported are an upset stomach, nausea, vomiting and diarrhoea, feeling unwell, “pins and needles”, difficulty concentrating, slow reactions, and dizziness (including dizziness or light-headedness on standing). Furosemide may cause raised blood levels of cholesterol, triglycerides and sugar, which can make diabetes worse, and can cause gout. There may be an increased tendency to thrombosis (clots in the blood vessels), especially in elderly patients. Patients with prostate problems may develop retention of urine. Premature infants may develop kidney stones or problems with the circulation of the blood within the heart.

Furosemide may also occasionally affect your blood production and composition. If you start getting mouth ulcers, a sore throat or repeated infections, or if you become anaemic (unusual tiredness or less of colour from the lining of the eyes or skin), or develop a tendency to bleed or bruise easily, tell your doctor. Liver problems including raised liver enzymes and
jaundice can develop (e.g. yellowing of the skin and/or whites of the eyes), and an inflamed, pancreas can occur (which may result in nausea and vomiting with pain the abdomen and back).

Very rarely furosemide can cause hearing disturbances including ringing in the ears.

Rarely, allergic reactions can occur. You should tell your doctor immediately if you develop a fever, pain in the joints, wheezing, difficulty breathing, a skin rash, itching, or swelling of your lips, eyes or tongue, become sensitive to sunlight, or collapse

Occasionally the area around where the needle is injected can become sore, red and itchy.

If you notice any side-effects not mentioned in this leaflet, or feel that the medicine is affecting you badly, please tell your doctor or nurse.

5. STORING FUROSEMIDE 10MG/ML SOLUTION FOR INJECTION OR INFUSION

Keep out of the reach and sight of children
Store in the original container
Do not use after the expiry date stated on the label
For single use. Discard any unused product immediately after use.

This leaflet was prepared in May 2006

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
   Furosemide 10mg/ml Solution for Injection or Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
   Each ml contains 10mg of furosemide.
   Each 2ml ampoule contains 20mg of furosemide.
   Each 25ml vial contains 250mg of furosemide.
   For excipients, see section 6.1.

3. PHARMACEUTICAL FORM
   Solution for injection or infusion
   The solution is colourless or almost colourless.

CLINICAL PARTICULARS

4.1 Therapeutic indications
   Furosemide 10mg/ml Injection is a diuretic indicated for use when a prompt and effective diuresis is required. The intravenous formulation is appropriate for use in emergencies or when oral therapy is precluded. Indications include cardiac, pulmonary, hepatic and renal oedema.

4.2 Posology and method of administration
   Route of administration: intramuscular or intravenous use.
   
   Adults
   Intravenous furosemide must be injected or infused slowly, a rate of 4 mg per minute must not be exceeded. In patients with severe impairment of renal function (serum creatinine >5 mg/dl), it is recommended that an infusion rate of 2.5 mg per minute is not exceeded.
   
   Intramuscular administration must be restricted to exceptional cases where neither oral nor intravenous administration are feasible. It must be noted that intramuscular injection is not suitable for the treatment of acute conditions such as pulmonary oedema.
   
   To achieve optimum efficacy and suppress counter-regulation, a continuous furosemide infusion is generally to be preferred to repeated bolus injections. Where continuous furosemide infusion is not feasible for follow-up treatment after one or several acute bolus doses, a follow-up regimen with low doses given at short intervals (approximately four hours) is to be preferred to a regimen with higher bolus doses at longer intervals.
   
   Doses of 20 to 80 mg intramuscularly or intravenously may be given initially. If larger doses are required, they should be given by 20 mg increments and not given more often than every two hours. If doses greater
than 50 mg are required it is recommended that they be given by slow intravenous infusion. The recommended maximum daily dose of furosemide administration is 1,500 mg.

**Elderly:** The dosage recommendations for adults apply, but in the elderly furosemide is generally eliminated more slowly. Dosage should be titrated until the required response is achieved.

**Children:** Parenteral doses for children range from 0.5 to 1.5 mg/kg bodyweight daily up to a maximum total daily dose of 20 mg.

4.3 **Contraindications**

Furosemide 10mg/ml injection 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 hypotension, pre-comatose and coma states associated with hepatic encephalopathy and breast feeding women.

Hypersensitivity to furosemide or any of the excipients of Furosemide 10mg/ml Injection. Patients allergic to sulphonamides may show cross-sensitivity to furosemide.

4.4 **Special warnings and precautions for use**

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.

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

Particularly careful monitoring is necessary in:

- patients with hypertension
- patients who are at risk from a pronounced fall in blood pressure
- patients where latent diabetes may become manifest or the insulin requirements of diabetic patients may increase
- patients with gout
- patients with hepatorenal syndrome
- patients with hypoprothrombinaemia, e.g. associated with nephrotoxic syndrome (the effect of furosemide may be weakened and its toxicity potentiated). Caution dose titration is required
- premature infants (possible development of nephrocalcinosis /nephrolithiasis, renal function must be monitored and renal ultrasonography performed)

Caution should be observed in patients liable to electrolyte deficiency. 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.

This medicinal product contains 0.25mol of sodium in a 2ml ampoule and 3.25mol in a 25ml vial. To be taken into consideration by patients on a controlled sodium diet.

4.5 **Interaction with other medicinal products and other forms of interaction**

The dosage of concurrently administered cardiac glycosides or anti-hypertensive agents may require adjustment. 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 inhibitor or increasing the dose of an ACE inhibitor.

The toxic effects of nephrotoxic antibiotics may be increased by concomitant administration of potent diuretics such as furosemide.

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

In common with other diuretics, serum lithium levels may be increased when lithium is given concomitantly with furosemide, resulting in increased lithium toxicity. Therefore, it is recommended that lithium levels are carefully monitored and where necessary the lithium dosage is adjusted in patients receiving this combination.

Certain non-steroidal anti-inflammatory agents (e.g. indomethacin, 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 sometimes attenuate the effects of other drugs (e.g. the effects of anti-diabetics and of pressor ammnes) and sometimes potentiate them (e.g. the effects of salicylates, theophylline and curare-type muscle relaxants).
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 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.

Concomitant administration of carbamazepine or aminoglutethimide may increase the risk of hypokalaemia.

Corticosteroids administered concurrently may cause sodium retention.

Corticosteroids, carbonic anhydrase inhibitors, cyclosporine, 5-alpha-reductase inhibitors in large amounts, prolonged use of laxatives, reboxetine and amphotericin may increase the risk of developing hypokalaemia.

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.

4.6. Pregnancy and lactation

Results of animal work, in general, show no hazardous effect of furosemide in pregnancy. There is clinical evidence of safety of the drug in the third trimester of human pregnancy; however, 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 may impair ability to drive or operate dangerous machinery.

4.8. Undesirable effects

Furosemide 10mg/ml Injection is generally well tolerated.

Eosinophilia is rare.

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

Bone marrow depression has been reported as a rare complication and necessitates withdrawal of treatment.

Rarely, paraesthesiae may occur.

Serum calcium levels may be reduced. In very rare cases tetany has been observed.

Nephrocalcinosis / Nephrolithiasis has been reported in premature infants.

Serum cholesterol and triglyceride levels may rise during furosemide treatment. During long term therapy they will usually return to normal within six months.

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.

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

Furosemide may cause a reduction in blood pressure which, if pronounced, may cause signs and symptoms such as impairment of concentration and reaction, light-headedness, sensations of pressure in the head, headache, dizziness, drowsiness, weakness, disorders of vision, dry mouth, orthostatic intolerance.
In isolated cases, intrahepatic cholestasis, an increase in liver transaminases or acute pancreatitis may develop.

The incidence of allergic reactions, such as skin rashes, photosensitivity, vasculitis, fever, interstitial nephritis or shock is very low, but when these occur treatment should be withdrawn. Skin and mucous membrane reactions may occasionally occur, e.g. itching, urticaria, other rashes or bullous lesions, erythema multiforme, exfoliative dermatitis, purpura.

As with other diuretics, electrolytes and water balance may be disturbed as a result of diuresis after prolonged therapy. 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, hypotension, confusion, muscle cramps, tetany, muscle weakness, disorders of cardiac rhythm and gastrointestinal symptoms. Pre-existing metabolic alkalosis (e.g. in decompensated cirrhosis of the liver) may be aggravated by furosemide treatment.

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.

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

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

Side-effects of a minor nature such as nausea, malaise or gastric upset (vomiting or diarrhoea) may occur but are not usually severe enough to necessitate withdrawal of treatment.

As with other diuretics, treatment with furosemide may lead to transient increases in blood creatinine and urea levels. Serum levels of uric acid may increase and attacks of gout may occur.

4.0. 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, fluid accumulation, 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 life-saving 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 designed to reduce absorption (e.g. activated charcoal).

PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

The available evidence from many experimental studies suggests that furosemide acts along the entire nephron with the exception of the distal convoluted tubule. The main effect is on the ascending limb of the loop of Henle with a complex effect on renal circulation. Blood flow is diverted from the juxta-medullary region to the outer cortex. The principal 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 is 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 overt within 4 hours. The optimal absorption site is the upper duodenum at pH 5.0. Regardless of route of administration, 85-90% 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 (80-85%), 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 applicable.

PHARMACEUTICAL PARTICULARS

5.1 List of excipients
Sodium chloride
Sodium hydroxide
Water for injections

5.2 Incompatibilities
Furosemide may precipitate out of solution in fluids of low pH (e.g. dextrose solutions).

5.3 Shelf life
Three years

5.4 Special precautions for storage
Store in the original package.

5.5 Nature and contents of container
Furosemide 10mg/ml Injection (20mg in 2ml)
Type I amber coloured glass ampoule (3ml capacity). Each pack contains 1, 5 or 10 ampoules*. 
Furosemide 10mg/ml Injection (250mg in 25ml)
Type I amber coloured glass ampoule (25ml capacity) sealed with a bromobutyl stopper, aluminium overseal and polypropylene flip-off cap. Each pack contains 1, 5 or 10 vials*. 

*Not all pack sizes may be marketed

5.6 Instructions for use and handling
From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately.

For single use only.
Furosemide 10mg/ml Injection solution should not be mixed with any other drugs in the injection bottle.

Intravenous furosemide must be injected or infused slowly, a rate of 4 mg per minute must not be exceeded. In patients with severe impairment of renal function (serum creatinine>5 mg/dl), it is recommended that an infusion rate of 2.5 mg per minute is not exceeded.

ADMINISTRATIVE DATA

7 MARKETING AUTHORISATION HOLDER
Wockhardt Uk Limited
Ash Road North
Wrexham
LL13 0UF
UK

7 MARKETING AUTHORISATION NUMBER
UKPAR Furosemide 10mg/ml Solution for Injection or Infusion

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
FUROSEMIDE 10 MG/ML SOLUTION FOR INJECTION OR INFUSION
PL 20851/0003

LABELLING

CARTON
UKPAR Furosemide 10mg/ml Solution for Injection or Infusion  

AMPOULE

Furosemide 10mg/ml Injection

20mg in 2ml

For iv or im injection or iv infusion

2ml

Windsor UK Limited, Windsor, UK

PL 20851/0003

Overprint Area
Furosemide 10mg/ml Solution for Injection or Infusion

PL 20851/0004

LABELLING

CARTON

For single use.

Discard any unused product immediately after use.

Keep out of reach of children.

Furosemide 10mg/ml Injection

Contains 250mg of furosemide in 25ml of solution.

Also contains sodium chloride, sodium hydroxide and water for injections.

Store in the original package.

Dose as directed by the physician. Please read the enclosed leaflet before use.

250mg in 25ml

For intravenous injection, intramuscular injection or administration by intravenous infusion in 1 vial.
Contains 250mg of furosemide in 25ml of solution.
Also contains sodium chloride, sodium hydroxide and water for injections.
Store in the original package.

Dose: as directed by the physician.
Please read the enclosed leaflet before use.
Keep out of the reach and sight of children
For single use. Discard any unused product immediately after use.

Furosemide 10mg/ml Injection

250mg in 25ml

For intravenous injection, intramuscular injection or administration by intravenous infusion.

Medicines Authorisation holder
Wockhardt UK Limited, Ash Road North,
Wrexham LL13 9UF, UK
PL 20851/004