

**FUROSEMIDE 20 MG/5 ML ORAL SOLUTION (FUROSEMIDE)
PL 20046/0037**

**FUROSEMIDE 40 MG/5 ML ORAL SOLUTION (FUROSEMIDE)
PL 20046/0038**

**FUROSEMIDE 50 MG/5 ML ORAL SOLUTION (FUROSEMIDE)
PL 20046/0039**

UKPAR

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**FUROSEMIDE 20 MG/5 ML ORAL SOLUTION (FUROSEMIDE)
PL 20046/0037**

**FUROSEMIDE 40 MG/5 ML ORAL SOLUTION (FUROSEMIDE)
PL 20046/0038**

**FUROSEMIDE 50 MG/5 ML ORAL SOLUTION (FUROSEMIDE)
PL 20046/0039**

LAY SUMMARY

The MHRA today granted Focus Pharmaceuticals Limited Marketing Authorisations (licences) for the medicinal products Furosemide 20mg/5ml Oral Solution (PL 20046/0037), Furosemide 40mg/5ml Oral Solution (PL 20046/0038) and Furosemide 50mg/5ml Oral Solution (PL 20046/0039). These prescription only medicines (POM) are diuretics, used to remove excess water from the body and are indicated in conditions including 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. Furosemide oral solution is recommended for use in patients requiring prompt diuresis who are unable to take solid dose forms.

Furosemide oral solution contains the active ingredient furosemide, which helps the kidneys get rid of water that is not needed in the body.

The clinical data presented to the MHRA, pre licensing, demonstrated that Furosemide 50mg/5ml Oral Solution is essentially similar or equivalent to the approved product, Lasix 10mg/ml Liquid and, as such, can be used interchangeably. Furosemide 20mg/5ml Oral Solution and Furosemide 40mg/5ml Oral Solution are different strengths of the same solution.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Furosemide 20mg/5ml Oral Solution, Furosemide 40mg/5ml Oral Solution and Furosemide 50mg/5ml Oral Solution outweigh the risks, hence Marketing Authorisations have been granted.

**FUROSEMIDE 20 MG/5 ML ORAL SOLUTION (FUROSEMIDE)
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PL 20046/0038**

**FUROSEMIDE 50 MG/5 ML ORAL SOLUTION (FUROSEMIDE)
PL 20046/0039**

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 20mg/5ml Oral Solution (PL 20046/0037), Furosemide 40mg/5ml Oral Solution (PL 20046/0038) and Furosemide 50mg/5ml Oral Solution (PL 20046/0039) to Focus Pharmaceuticals Limited on 1 December 2005. The products are prescription only medicines.

The applications were submitted as abridged applications according to article 10.1(a)(iii) of Directive 2001/83/EC, claiming essential similarity to the original product Lasix 10mg/ml Liquid.

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 20mg/5ml Oral Solution, Furosemide 40mg/5ml Oral Solution and Furosemide 50mg/5ml Oral Solution were submitted at the same time and were assessed simultaneously. Consequently, all sections of this Scientific Discussion refer to all three products.

PHARMACEUTICAL ASSESSMENT

PL NUMBER: 20046/0037-39
PRODUCT: Furosemide 20 mg/5 ml Oral Solution
Furosemide 40 mg/5 ml Oral solution
Furosemide 50 mg/5 ml Oral solution
ACTIVE: Furosemide
COMPANY: Focus Pharmaceuticals Ltd.
LEGAL STATUS: POM

REQUESTS FOR INSPECTION ACTION PRIOR TO AUTHORISATION

Not applicable.

INTRODUCTION

These are national, abridged, standard applications for Furosemide 20 mg/5 ml, 40 mg/5 ml and 50 mg/5 ml Oral Solution submitted under article 10.1 (a) (iii) first and last paragraph of Directive 2001/83/EC on the basis of different strengths (20 mg/5 ml and 40 mg/5 ml) in relation to the innovator product, Lasix 10 mg/ml Liquid (Hoechst Marion Roussel PL: 13402/0019) first authorised on 09/06/1993. As these applications are for oral solutions no bioequivalence data are required.

Furosemide is a loop diuretic which inhibits sodium and chloride reabsorption at the Loop of Henle. When oral doses of furosemide are given to normal subjects mean bioavailability of the drug is approximately 52 %. Furosemide extensively binds to plasma protein. Renal excretion and elimination by metabolism plus faecal excretion contribute equally to plasma clearance. Furosemide is indicated in all conditions requiring prompt diuresis including cardiac, pulmonary, hepatic and renal oedema and peripheral oedema.

DRUG SUBSTANCE

GENERAL INFORMATION

The active substance is described by a monograph of the Ph. Eur. The application refers to a manufacturer whose EDMF has been previously assessed by the MHRA.

Nomenclature

Recommended International Nonproprietary Name (INN): Furosemide

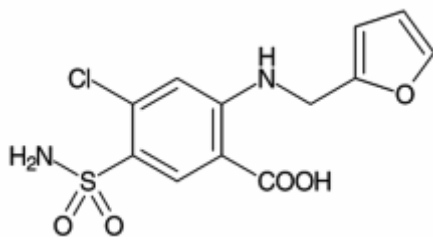
Compendial Name: Furosemide

Chemical Name:

4-chloro-2-(furfurylamino)-5-sulfamoylbenzoic acid (Ph. Eur.);

4-chloro-N-furfuryl-5-sulfamoylanthranilic acid (USP);

Structure



C₁₂H₁₁ClN₂O₅

Mw: 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.

Manufacture

Manufacturer (DSM)

These applications refer to the EDMF Version 2, June 2004. The open part is provided in the dossier. This EDMF has been assessed previously by the MHRA. Only where significant changes have been made since the last assessment will comment be made in the report. It is noted that the DSM supplies the active substance for a large number of currently licensed UK products.

Description of Manufacturing Process and Process Controls

No significant changes.

Control of Materials

No significant changes.

Controls of Critical Steps and Intermediates

No significant changes.

Process Validation and/or Evaluation

No significant changes.

Manufacturing Process Development

No significant changes.

Characterisation

Elucidation of Structure and other Characteristics

Characterisation is performed using NMR, IR and UV. Comparison is made with EP and USP reference standards. This is acceptable.

Discussion of physical characteristics such as particle size and polymorphism is provided. However, because the drug product is an oral solution, control of these parameters is unnecessary.

Impurities

Impurities listed include the 5 Ph. Eur. impurities and 2 potential process impurities.

Control of Drug Substance

Specification

An appropriate specification is provided for quality control of furosemide.

Analytical Procedures

The DSM uses compendial methods to control the drug substance. These are described.

Validation of Analytical Procedures

Not applicable

Batch Analyses

Batch analytical data are provided which conform to Ph. Eur. requirements.

Comparative batch analytical data from the DSM and FPM for a batch of the drug substance used in product development is provided and shows similar and compliant results.

Justification of Specification

Specifications are in line with pharmacopoeia.

Reference Standards or Materials

No significant change.

Container Closure System

No significant change.

Stability

Stability Summary and Conclusions

Stability data are presented to support a re-test period of 60 months. Drug substance is packed in scaled-down commercial packaging and stored/tested according to ICH guidelines (long-term, intermediate and accelerated testing).

Along with the 60 month re-test period the storage statement 'Preserve in well closed, light-resistant containers' is proposed.

Post-Approval Stability Protocol and Stability Commitment

The stability protocol includes a commitment to include one further batch on stability testing every year. Furthermore, the DSM states that should significant changes be made to the process/method additional stability testing will be performed. This is acceptable.

Stability Data

All data indicate the inherent stability of the drug substance.

DRUG PRODUCT

Description and Composition of the Drug Product

Furosemide 20mg/5ml Oral Solution: Clear yellow oral solution with a cherry odour and taste

Furosemide 40mg/5ml Oral Solution: Clear oral solution with a cherry odour and taste

Furosemide 50mg/5ml Oral Solution: Clear oral solution with a cherry odour and taste

Active							
	Components	Quantity per 5 ml	Quantity per 5 ml	Quantity per 5ml	Unit	Function	Quality standard
1	Furosemide	20.00	40.00	50.00	mg		Ph.Eur

Qualitative Composition of Furosemide Oral Solution

	Components	Function	Quality standard
1	Furosemide		Ph.Eur
2	Liquid maltitol	Vehicle/Sweetener	Ph.Eur
3	Ethanol (96%)	Solvent/Preservative	Ph.Eur
4	Disodium hydrogen phosphate dodecahydrate	Buffer	Ph.Eur
5	Sodium hydroxide 32 % w/w soln.	pH adjuster/ Active solubiliser	Ph.Eur
6	Citric acid monohydrate	Buffer	Ph.Eur
7	Flavour cherry	Flavour	HSE
8	Quinoline yellow E104*	Colour	HSE
9	Purified water	Vehicle and solvent	Ph.Eur

*Only present in Furosemide 20mg/5ml oral solution

The product is packaged in type III amber glass (150 ml) bottles with a PP child resistant closure (LDPE liner).

Pharmaceutical Development

Components of the Drug product

Drug Substance

The drug substance is supplied in compliance with the Ph. Eur. monograph. Further control of physical characteristics are unnecessary since the product is a solution. The applicant refers to qualitative information for the innovator product and a similar generic product (Frusol Oral Solution - Rosemount) to infer the compatibility of the

drug substance and excipients and indicates that this is further demonstrated by finished product stability data. This is acceptable.

Excipients

A brief summary of the choice of excipients and their suitability is provided. All are common to oral solutions and are used in similar generic products.

Drug Product

Formulation development

This was focused on formulating a product essentially similar to the UK innovator product Lasix 10 mg/ml. Development was performed at laboratory scale and characterised in comparison with Lasix prior to the manufacture of pilot scale batches. The dossier also makes reference to published data on other furosemide solutions that was used in the development. The qualitative composition of the test product is similar to Frusol Oral solutions also currently licensed in the UK.

The results of preservative efficacy testing are discussed later in the report. Lab scale batches demonstrated similar profiles for assay and impurities with comparative innovator products.

Physicochemical and biological properties

Not applicable.

Manufacturing Process Development

The manufacturing process is very straightforward. A brief description is provided.

Container Closure System

The primary packaging is common for this type of product.

Microbiological Attributes

The applicant indicates that on the basis of the results of preservative efficacy testing a further preservative system is not required due to the presence of ethanol in the formulation.

Compatibility

There are not considered to be compatibility issues with this product.

Manufacture

Batch Formula

The batch formula for each strength is presented for manufacturing batches of a maximum of 1,000 L

Description of Manufacturing Process and Process Controls

This is a simple manufacturing process, the details of which are included in the process validation section.

Control of Critical Steps and Intermediates

No intermediates are generated and critical steps are controlled with suitable in-process controls

Process Validation and/or Evaluation

Acceptable process validation was performed during the manufacture of batches for all three strengths of the product. A formal process validation protocol to be conducted on production scale batches in line with Annex 1 CPMP guideline QWP/848/96 has been provided.

Control of Excipients

Specifications

Ethanol, disodium hydrogen orthophosphate dodecahydrate, citric acid, liquid maltitol and purified water are controlled according to their respective Ph. Eur. monographs. Test specifications for sodium hydroxide 32 % w/w solution are provided. Cherry flavouring and the Quinoline Yellow (E104) colouring are tested according to in-house specifications. Copies of the specification and representative certificates of analysis from the suppliers have been provided. Confirmation that the excipients comply with appropriate EC requirements is provided.

Supportive certificates of analysis and TSE statements have been provided for all excipients.

Analytical Procedures

Excipients are tested by Ph. Eur. methods or standard chemical and physical tests for which validation is not required.

Excipients of Human or Animal Origin

None (see above).

Control of Drug Product

Specification

The finished product specification proposed is acceptable.

Analytical Procedures

Details of the analytical testing methods have been provided and are acceptable.

Validation of Analytical Procedures

The analytical procedures used have been suitably validated.

Batch Analyses

Batch analytical data is provided and all batches comply with the finished product specifications. Levels of impurities are not detectable at release.

Characterisation of Impurities

The impurities are characterised in full.

Justification of Specification(s)

The specifications are suitable for a product of this type.

Reference Standards or Materials

The reference standards used are USP reference samples.

Container Closure System

Bottle: Type III amber glass bottle.

Closure: Polypropylene child resistant closure with LDPE liner.

Test specifications to be performed on glass bottles prior to qualification of a supplier are provided. An example of a certificate of conformance for the bottle is provided and shows conformance with the relevant Ph Eur requirements for a type III glass bottle.

Specifications and certificates of analysis for the polypropylene lids are provided.

Stability

Stability Summary and Conclusion

A preliminary 3 month accelerated stability study was performed on lab scale batches. Further to this stability testing was conducted with pilot scale batches.

The final product placed on stability was packaged as intended for market under ICH conditions 25°C/60%RH (up to 36 months) and 40°C/75% RH (6 months). Currently, only 12 months long-term and 6 months accelerated data are available. An In-use stability study has been performed in line with CPMP Guideline QWP/2934/99 and is acceptable.

An 18-month shelf-life is requested with the storage instruction 'Do not store above 25 °C'. This is considered acceptable on the basis of the available stability data.

Post-approval Stability Protocol and Stability Commitment

A commitment to perform stability testing on the first two commercial batches of each strength according to ICH long term, intermediate and accelerated conditions is provided. This is acceptable given the similarity of the formulations.

ASSESSOR'S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET

The SPC, PIL and Labels are pharmaceutically acceptable.

Essential similarity

The applicant claims essential similarity to the innovator product Lasix 10 mg/ml. The test product is presented as three different strengths, the highest being 50 mg/5 ml. Because the product is an oral solution and the SPC posology is similar to that of the innovator product (no specific reference to the different strengths) this is acceptable.

Administrative

Comment on Expert report

The expert report provides a useful, if non-critical, summary of the dossier and is acceptable.

GMP

Suitable manufacturing authorisations have been provided to ensure the product is manufactured according to the principles of GMP.

Guideline Compliance

In general the dossier is in line with current guidelines.

ASSESSOR's OVERALL CONCLUSIONS ON QUALITY AND ADVICE

In general the dossier is well presented. The supplier of the drug substance is used in a number of currently licensed UK products. The manufacturing process is straightforward and the drug product is well controlled.

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 an application of this type.

CLINICAL ASSESSMENT

1. INTRODUCTION

This is a generic application for furosemide liquid. The reference product is Lasix Liquid 10mg/ml (PL – 13402/0019, Hoechst Marian Roussel).

2. BACKGROUND

ATC code C03C A01 High Ceiling Diuretics – Sulfonamides Plain

3. INDICATIONS

“Furosemide Liquid is a diuretic recommended for use in all indications when a prompt and effective diuresis is required in patients who are unable to take solid dose forms. Indications include cardiac, pulmonary, hepatic and renal oedema, peripheral oedema due to mechanical obstruction or venous insufficiency or hypertension.”

4. DOSE & DOSE SCHEDULE

“Furosemide Liquid has an exceptionally wide therapeutic range, the effect being proportional to the dosage. Furosemide Liquid is best given as a single dose either daily or on alternate days.

The usual initial daily dose is 40mg. This may require adjustment until the effective dose is achieved as a maintenance dose. In mild cases, 20mg daily or 40mg 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 daily, or intermittently. Severe cases may require gradual titration of the furosemide dosage up to 600mg daily. 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: Oral doses for children range from 1 to 3mg/kg body weight daily up to a maximum total dose of 40 mg/day”.

5. TOXICOLOGY

Toxicological profile of furosemide is well known. There is an extensive experience from its use in humans.

6. CLINICAL PHARMACOLOGY

The clinical pharmacology of furosemide is very well known as the product has been in clinical use for many years.

6.1 BIOEQUIVALENCE

No bioequivalence study has been submitted. The clinical expert in the overview states that as Furosemide oral solutions are simple solutions and no absorption-modifying agents are included in the formulation, no untoward issues related to bioavailability therefore arise.

7. EFFICACY

No new clinical efficacy data has been submitted and none is required. Efficacy of furosemide is well known.

8. SAFETY

The safety of furosemide is well known as it has been in clinical use for many years. No new data has been submitted and none is required.

9. EXPERT REPORT

The clinical expert report was written by an appropriately qualified medical advisor.

10. SUMMARY OF PRODUCT CHARACTERISTICS

The SPC is satisfactory.

11. PATIENT INFORMATION LEAFLET

Patient information leaflet is satisfactory.

12. LABELLING

Medically satisfactory.

13. DISCUSSION

Furosemide is a well known drug and has been used clinically for many years. Its clinical use and safety profile is well defined. No safety and efficacy data has been submitted and none is required. As it is a liquid preparation for oral administration and it has no excipient which alters gastrointestinal absorption, no bioequivalence study has been done and none is required.

14. CONCLUSIONS

There is no clinical objection to the grant of marketing authorisation for these preparations.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Furosemide 20mg/5ml oral solution, Furosemide 40mg/5ml oral solution and Furosemide 50mg/5ml oral solution 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.

**FUROSEMIDE 20 MG/5 ML ORAL SOLUTION (FUROSEMIDE)
PL 20046/0037**

**FUROSEMIDE 40 MG/5 ML ORAL SOLUTION (FUROSEMIDE)
PL 20046/0038**

**FUROSEMIDE 50 MG/5 ML ORAL SOLUTION (FUROSEMIDE)
PL 20046/0039**

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 15/09/2004.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 25/10/2004.
3	Following assessment of the application the MHRA requested further information relating to the quality dossier on 24/03/2005 and again on 04/08/2005.
4	The applicant responded to the MHRA's requests, providing further information on 09/06/2005 and 08/09/2005.
5	Following assessment of the response the MHRA requested further additional information relating to the clinical dossier on 18/04/2005
6	The applicant responded, providing further information, on 03/05/2005
7	The application was determined on 01/12/2005

**FUROSEMIDE 20 MG/5 ML ORAL SOLUTION (FUROSEMIDE)
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**FUROSEMIDE 40 MG/5 ML ORAL SOLUTION (FUROSEMIDE)
PL 20046/0038**

**FUROSEMIDE 50 MG/5 ML ORAL SOLUTION (FUROSEMIDE)
PL 20046/0039**

STEPS TAKEN FOR ASSESSMENT

Date submitted	Application type	Scope	Outcome

**FUROSEMIDE 20 MG/5 ML ORAL SOLUTION (FUROSEMIDE)
PL 20046/0037**

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Furosemide 20mg/5ml Oral Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml contains 20mg Furosemide.
For excipients, see Section 6.1

3. PHARMACEUTICAL FORM

Oral solution.
A yellow, clear solution with odour of cherries.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Furosemide 20mg/5ml Oral Solution is a diuretic recommended for use in all indications when a prompt and effective diuresis is required in patients who are unable to take solid dose forms. Indications include cardiac, pulmonary, hepatic and renal oedema, peripheral oedema due to mechanical obstruction or venous insufficiency or hypertension.

4.2 Posology and Method of Administration

Furosemide 20mg/5ml Oral Solution has an exceptionally wide therapeutic range, the effect being proportional to the dosage. Furosemide 20mg/5ml Oral Solution is best given as a single dose either daily or on alternate days.

The usual initial daily dose is 40 mg. This may require adjustment until the effective dose is achieved as a maintenance dose. 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 daily. 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: Oral doses for children range from 1 to 3 mg/kg body weight daily up to a maximum total dose of 40 mg/day.

4.3 Contra-Indications

Furosemide 20mg/5ml Oral Solution 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 20mg/ml Oral Solution. Patients allergic to sulphonamides may show cross-sensitivity to furosemide.

This product contains liquid maltitol and should not be taken by patients with the rare hereditary problem of fructose intolerance.

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.
- who are at risk from a pronounced fall in blood pressure.
- where latent diabetes may become manifest or the insulin requirements of diabetic patients may increase.
- with gout.
- with hepatorenal syndrome.
- 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).

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 ethanol 10% v/v (alcohol) –each dose contains up to 0.5ml per dose and should be used with care in those suffering from alcoholism. To be taken into account in pregnant or breast feeding women, children and high-risk groups such as patients with liver disease or epilepsy.

4.5 Interactions with other Medicaments 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 effects of certain drugs which have inherent anti-hypertensive effects will be potentiated with furosemide.

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

Oral furosemide and sucralfate must not be taken within two hours of each other because sucralfate decreases the absorption of furosemide from the intestine and so reduced its effect.

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. anti-arrhythmics, Terfenadine, certain anti-psychotics e.g. Amisulpride, 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, Reboxetine, Amphotericin, B2 sympathomimetics in large amounts, and prolonged use of laxatives 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.

Concomitant treatment with certain other drugs may cause an enhanced hypotensive effect e.g. Aldeskleukin, Alprostadil and Amifostine.

4.6 Pregnancy and Lactation

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 20mg/5ml Oral Solution 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.

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.

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

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

ATC code: C03C A01

Furosemide is a loop diuretic.

5.2 Pharmacokinetic Properties

Furosemide is a weak carboxylic acid which exists mainly in the dissociated form in the gastro-intestinal tract. Furosemide is rapidly but incompletely absorbed (60-70%) on oral administration and its effect is largely over within four 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 four hours after the drug is given. 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.

5.3 Preclinical Safety Data

Furosemide is a widely used diuretic which has been available for over thirty years and its safety profile in man is well established.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sodium hydroxide 32% w/w/ solution
Disodium hydrogen orthophosphate dodecahydrate
Citric acid monohydrate
Maltitol liquid
Cherry flavour
Quinoline yellow (E104)
Ethanol (96% v/v)
Purified water.

6.2 Incompatibilities

Not applicable.

6.3. Shelf Life

18 months unopened.
Once opened, use within 3 months.

6.4. Special Precautions for Storage

Do not store above 25°C.
Store in the original package.

6.5. Nature and Contents of Container

Amber glass (type III, Ph Eur) bottle with polypropylene screw cap containing 150ml.

6.6. Instruction for Use/Handling

None.

7. MARKETING AUTHORISATION HOLDER

Focus Pharmaceuticals Ltd.
Unit 5, Faraday Court
First Avenue
Centrum 100
Burton upon Trent
Staffordshire
DE14 2WX

8. MARKETING AUTHORISATION NUMBER

PL 20046/0037

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/12/2005

10. DATE OF REVISION OF THE TEXT

**FUROSEMIDE 40 MG/5 ML ORAL SOLUTION (FUROSEMIDE)
PL 20046/0038**

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Furosemide 40mg/5ml Oral Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml contains 40mg Furosemide.
For excipients, see Section 6.1

3. PHARMACEUTICAL FORM

Oral solution.
A clear solution with odour of cherries.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Furosemide 40mg/5ml Oral Solution is a diuretic recommended for use in all indications when a prompt and effective diuresis is required in patients who are unable to take solid dose forms. Indications include cardiac, pulmonary, hepatic and renal oedema, peripheral oedema due to mechanical obstruction or venous insufficiency or hypertension.

4.2 Posology and Method of Administration

Furosemide 40mg/5ml Oral Solution has an exceptionally wide therapeutic range, the effect being proportional to the dosage. Furosemide 40mg/5ml Oral Solution is best given as a single dose either daily or on alternate days.

The usual initial daily dose is 40 mg. This may require adjustment until the effective dose is achieved as a maintenance dose. 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 daily. 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: Oral doses for children range from 1 to 3 mg/kg body weight daily up to a maximum total dose of 40 mg/day.

4.3 Contra-Indications

Furosemide 40mg/5ml Oral Solution 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 40 mg/5ml Oral Solution. Patients allergic to sulphonamides may show cross-sensitivity to furosemide.

This product contains liquid maltitol and should not be taken by patients with the rare hereditary problem of fructose intolerance.

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.
- who are at risk from a pronounced fall in blood pressure.
- where latent diabetes may become manifest or the insulin requirements of diabetic patients may increase.
- with gout.
- with hepatorenal syndrome.
- 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).

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 ethanol 10% v/v (alcohol) –each dose contains up to 0.5ml per dose and should be used with care in those suffering from alcoholism. To be taken into account in pregnant or breast feeding women, children and high-risk groups such as patients with liver disease or epilepsy.

4.5 Interactions with other Medicaments 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 effects of certain drugs which have inherent anti-hypertensive effects will be potentiated with furosemide.

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

Oral furosemide and sucralfate must not be taken within two hours of each other because sucralfate decreases the absorption of furosemide from the intestine and so reduced its effect.

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. anti-arrhythmics, Terfenadine, certain anti-psychotics e.g. Amisulpride, 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, Reboxetine, Amphotericin, B2 sympathomimetics in large amounts, and prolonged use of laxatives 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.

Concomitant treatment with certain other drugs may cause an enhanced hypotensive effect e.g. Aldeskleukin, Alprostadil and Amifostine.

4.6 Pregnancy and Lactation

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 40mg/5ml Oral Solution 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.

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.

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

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

ATC code: C03C A01

Furosemide is a loop diuretic.

5.2 Pharmacokinetic Properties

Furosemide is a weak carboxylic acid which exists mainly in the dissociated form in the gastro-intestinal tract. Furosemide is rapidly but incompletely absorbed (60-70%) on oral administration and its effect is largely over within four 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 four hours after the drug is given. 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.

5.3 Preclinical Safety Data

Furosemide is a widely used diuretic which has been available for over thirty years and its safety profile in man is well established.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Sodium hydroxide 32%w/w/ solution
Disodium hydrogen orthophosphate dodecahydrate
Citric acid monohydrate
Maltitol liquid
Cherry flavour
Ethanol (96%v/v)
Purified water.

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

18 months unopened.
Once opened, use within 3 months.

6.4. Special Precautions for Storage

Do not store above 25°C.
Store in the original package.

6.5. Nature and Contents of Container

Amber glass (type III, Ph Eur) bottle with polypropylene screw cap containing 150ml.

6.6. Instruction for Use/Handling

None.

7. MARKETING AUTHORISATION HOLDER

Focus Pharmaceuticals Ltd.
Unit 5, Faraday Court
First Avenue
Centrum 100
Burton upon Trent
Staffordshire
DE14 2WX

8. MARKETING AUTHORISATION NUMBER

PL 20046/0038

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

01/12/2005

10. DATE OF REVISION OF THE TEXT

**FUROSEMIDE 50 MG/5 ML ORAL SOLUTION (FUROSEMIDE)
PL 20046/0039**

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Furosemide 50mg/5ml Oral Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml contains 50mg Furosemide.
For excipients, see Section 6.1

3. PHARMACEUTICAL FORM

Oral solution.
A clear solution with odour of cherries.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Furosemide 50mg/5ml Oral Solution is a diuretic recommended for use in all indications when a prompt and effective diuresis is required in patients who are unable to take solid dose forms. Indications include cardiac, pulmonary, hepatic and renal oedema, peripheral oedema due to mechanical obstruction or venous insufficiency or hypertension.

4.2 Posology and Method of Administration

Furosemide 50mg/5ml Oral Solution has an exceptionally wide therapeutic range, the effect being proportional to the dosage. Furosemide 50mg/5ml Oral Solution is best given as a single dose either daily or on alternate days.

The usual initial daily dose is 40 mg. This may require adjustment until the effective dose is achieved as a maintenance dose. 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 daily. 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: Oral doses for children range from 1 to 3 mg/kg body weight daily up to a maximum total dose of 40 mg/day.

4.3 Contra-Indications

Furosemide 50mg/5ml Oral Solution 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 50mg/5ml Oral Solution. Patients allergic to sulphonamides may show cross-sensitivity to furosemide.

This product contains liquid maltitol and should not be taken by patients with the rare hereditary problem of fructose intolerance.

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.
- who are at risk from a pronounced fall in blood pressure.
- where latent diabetes may become manifest or the insulin requirements of diabetic patients may increase.
- with gout.
- with hepatorenal syndrome.
- 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).

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 ethanol 10% v/v (alcohol) –each dose contains up to 0.5ml per dose and should be used with care in those suffering from alcoholism. To be taken into account in pregnant or breast feeding women, children and high-risk groups such as patients with liver disease or epilepsy.

4.5 Interactions with other Medicaments 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 effects of certain drugs which have inherent anti-hypertensive effects will be potentiated with furosemide.

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

Oral furosemide and sucralfate must not be taken within two hours of each other because sucralfate decreases the absorption of furosemide from the intestine and so reduced its effect.

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. anti-arrhythmics, Terfenadine, certain anti-psychotics e.g. Amisulpride, 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, Reboxetine, Amphotericin, B2 sympathomimetics in large amounts, and prolonged use of laxatives 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.

Concomitant treatment with certain other drugs may cause an enhanced hypotensive effect e.g. Aldeskleukin, Alprostadil and Amifostine.

4.6 Pregnancy and Lactation

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 50mg/5ml Oral Solution 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.

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.

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

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

ATC code: C03C A01

Furosemide is a loop diuretic.

5.2 Pharmacokinetic Properties

Furosemide is a weak carboxylic acid which exists mainly in the dissociated form in the gastro-intestinal tract. Furosemide is rapidly but incompletely absorbed (60-70%) on oral administration and its effect is largely over within four 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 four hours after the drug is given. 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.

5.3 Preclinical Safety Data

Furosemide is a widely used diuretic which has been available for over thirty years and its safety profile in man is well established.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sodium hydroxide 32% w/w solution
Disodium hydrogen orthophosphate dodecahydrate
Citric acid monohydrate
Maltitol liquid
Cherry flavour
Ethanol (96% v/v)
Purified water

6.2 Incompatibilities

Not applicable.

6.3. Shelf Life

18 months unopened.
Once opened, use within 3 months.

6.4. Special Precautions for Storage

Do not store above 25°C.
Store in the original package.

6.5. Nature and Contents of Container

Amber glass (type III, Ph Eur) bottle with polypropylene screw cap containing 150ml.

6.6. Instruction for Use/Handling

None.

7. MARKETING AUTHORISATION HOLDER

Focus Pharmaceuticals Ltd
Unit 5, Faraday Court
First Avenue
Centrum 100
Burton upon Trent
Staffordshire
DE14 2WX

8. MARKETING AUTHORISATION NUMBER

PL 20046/0039

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/12/2005

10. DATE OF REVISION OF THE TEXT

**FUROSEMIDE 20 MG/5 ML ORAL SOLUTION (FUROSEMIDE)
PL 20046/0037**

**FUROSEMIDE 40 MG/5 ML ORAL SOLUTION (FUROSEMIDE)
PL 20046/0038**

**FUROSEMIDE 50 MG/5 ML ORAL SOLUTION (FUROSEMIDE)
PL 20046/0039**

PRODUCT INFORMATION LEAFLET

Package leaflet
**Furosemide 20, 40 &
50mg/5ml Oral Solution**

Read this leaflet carefully before you start taking this medicine.
Keep this leaflet; you may need to read it again.
If you have further questions or you are not sure about anything, ask your doctor or pharmacist.
This medicine is for you personally and should not be given to anyone else. It may harm them, even if their symptoms are the same as yours.

About your medicine

Your medicine is called Furosemide 20, 40 or 50mg/5ml Oral Solution.
Furosemide is part of a group of medicines called diuretics which are used to get rid of excess water in your body.

What is in your medicine?

Each 5ml of Furosemide Oral Solution contains 20, 40 or 50mg of the active ingredient furosemide. The inactive ingredients are ethanol 10% v/v, sodium hydroxide, disodium hydrogen orthophosphate dodecahydrate, citric acid (monohydrate), maltitol liquid, cherry flavour, quinoline yellow (E104) 20mg strength only) and purified water.

Furosemide 20mg/5ml oral solution is a clear, yellow, cherry-flavoured oral solution.
Furosemide 40 and 50mg/5ml oral solutions are clear, colourless, cherry-flavoured oral solutions.
Furosemide 20, 40 or 50mg/5ml oral solutions come in an amber glass bottle containing 150ml oral solution.

Who makes your medicine?

Your Furosemide 20, 40 or 50mg/5ml oral solution is made by Dales Pharmaceuticals Ltd, Keighley Road, Skipton, N. Yorks BD23 2RW.
The marketing authorisation holder is Focus Pharmaceuticals Ltd, Unit 5, Faraday Court, First Avenue, Burton upon Trent, Staffs, DE14 2WQ.

What is your medicine used for?

You may have a condition which affects your heart, lungs, kidneys, liver, blood vessels or blood pressure which may lead to a build up of water in your body. Furosemide is used where there is too much water in your body. The medical term for this is 'oedema'. Furosemide helps your kidneys to get rid of water that is not needed in your body.

Before you take your medicine

Do not take your medicine if you:

- have ever had a bad reaction to any of the ingredients listed in the 'What is in your medicine' section;
- have ever had a bad reaction to sulphonamides (drugs used to treat certain infections);
- have been told by your doctor that you have an intolerance to some sugars;
- are dehydrated or have lost a lot of blood;
- have kidney failure;

- have a severe lack of potassium in your blood which will make your muscles feel weak or may have paralysis;
- have a severe loss of sodium in your blood which may be caused by excessive sweating, vomiting or drug interaction;

- pre-coma and coma associated with liver failure;
- are breast-feeding.

Tell your doctor before you start to take your medicine if you:

- are pregnant or may become pregnant;
- have difficulty passing urine;
- have low blood pressure;
- have diabetes;
- have gout;
- have kidney problems as a result of liver disease;

Your doctor will want to give you a check up from time to time and do blood tests while you are taking this medicine.

Tell your doctor if you are taking, or have recently taken any of the following medicines:

- Digoxin for your heart; your doctor may need to change your dose.
- Drugs to lower blood pressure (eg: beta-blockers, calcium channel blockers, alpha-blockers and even vasodilators), particularly ACE inhibitors, as furosemide may cause your blood pressure to fall too low. Your doctor may need to change your dose of furosemide.
- Antibiotics for infections as some can affect your kidneys; furosemide can make this effect worse.
- Sucralfate to treat stomach ulcers. Do not take furosemide within two hours of taking sucralfate as furosemide will not work as well.
- Lithium, for depression or mania, as its effect may be increased. Your doctor will check your lithium levels and may change your dose.
- NSAIDs (nonsteroidal anti-inflammatory drugs) such as indomethacin, to treat inflammation or pain, as they can reduce the effect of furosemide.
- Aspirin as furosemide may increase its side effects.
- Medicines to control diabetes or raise blood pressure as they may not work as well when you take furosemide.
- Aminoglycosides eg: gentamicin used to treat serious infections, as the risk of side effects from either gentamicin or furosemide is greater. Furosemide will only be used if considered essential by your doctor.
- Cisplatin, a cancer treatment, as furosemide may increase the side effects of these drugs. Your doctor may change your dose of furosemide.
- Phenytoin, for epilepsy, as furosemide may not work as well.
- Carbamazepine, for epilepsy, as it may increase the side effects of furosemide if taken together.
- Corticosteroids used to treat inflammation or allergic reactions, carbenclozone to treat ulcers, reboxetine for depression, amphotericin for fungal infections, laxatives used over a long period or certain treatments for asthma when taken in large amounts. Your salt balance may be altered causing muscle weakening.
- Probenecid for gout or methotrexate for rheumatism or psoriasis, as furosemide will not

work as well or the effect of probenecid or methotrexate may be increased.

- Aldeskleukin, and Amifostine for treatment of cancer Alprostadil for impotence as they may lower your blood pressure.
 - Any other medicines not listed above.
- If the answer to any of these questions is YES, tell your doctor or pharmacist.

Other special warnings:

- If you feel drowsy or have blurred vision when you take Furosemide 20, 40 or 50mg/5ml oral solution, do not drive or operate machinery until these effects have worn off;
- Your medicine contains 10% v/v ethanol (alcohol) ie: up to 31mg alcohol per 5ml medicine, equivalent to approximately 10ml beer, 4ml wine per 5ml medicine. Take advice from your doctor if you have liver disease or epilepsy, or have a problem with alcoholic drink.

If you become pregnant while taking furosemide, your doctor will need to check the growth of your baby.

Furosemide passes into breast milk, it can also stop you producing milk; DO NOT breast feed if you are being treated with Furosemide.

Furosemide 20, 40 or 50mg/5ml Oral Solution contains sodium:

Furosemide 20mg/5ml Oral Solution contains approximately 12mg sodium per 5ml medicinal product.
Furosemide 40mg/5ml Oral Solution contains approximately 15mg sodium per 5ml medicinal product.
Furosemide 50mg/5ml Oral Solution contains approximately 16mg sodium per 5ml medicinal product.

Tell your doctor if you are on a controlled sodium diet. If you see another doctor or visit a hospital, remember to tell them what medicines you are already taking.

How to take your medicine

It is important to take your medicine at the right times. You must take it as instructed by your doctor. Furosemide 20, 40 or 50mg/5ml Oral Solution is normally taken once a day, normally in the morning.

Adults The dosage is increased gradually, starting with doses of 40mg once a day. In mild cases, 20mg daily or 40mg on alternate days may be sufficient. Your doctor will decide your final dose, depending upon how you respond. The maximum dose of furosemide is 1500mg daily.

Elderly Your doctor will start you on a low dose and gradually increase it until you respond to the medicine.

Children The dosage depends on the weight of your child. A dose range of 1-3mg/kg body weight up to a maximum of 40mg daily is permitted. Your doctor will tell you the actual dose for your child depending upon their response.

If you are not sure how much medicine to take, ask your doctor or pharmacist.

Do not stop taking Furosemide 20, 40 or 50mg/5ml Oral Solution without speaking to your doctor first. He/she will tell you how to reduce your dose before stopping completely.

If you forget to take a dose

If you forget to take a dose at the right time, take it as soon as you remember. Do not take two doses

together. If it is almost time to take the next dose, wait until then and then carry on as before.

If you take more Furosemide 20, 40 or 50mg/5ml Oral Solution than you should

Contact the nearest hospital casualty department or a doctor for advice if you have swallowed too much Furosemide 20, 40 or 50mg/5ml Oral Solution or if you think a child has accidentally swallowed any.

Take this leaflet and any Furosemide 20, 40 or 50mg/5ml Oral Solution that you still have to show the doctor.

Whilst taking your medicine

You may have some side effects while you are taking your medicine. The following side effects are rare. Tell your doctor immediately if you have:

- Increased sensitivity to touch, skin pricking;
- Spasms, muscle twitching and cramps;
- Kidney stones in premature infants;
- Inflammation of the pancreas;
- Jaundice: your skin will appear yellow;
- Hearing problems or ringing in your ears (tinnitus);
- Allergic reactions such as skin rashes, sensitivity to light, purple spotting of the skin, fever or shock. If these occur stop taking your medicine and consult your doctor;
- Severe allergic reactions such as anaphylactic or anaphylactoid reactions (egg shock).

Furosemide can occasionally cause changes in your blood; your doctor will perform regular blood tests to ensure no changes have occurred. The symptoms of these changes include anaemia leading to tiredness and lethargy; unusual bleeding or bruising, blood slow to clot; lesions in your throat, mouth or skin.

Other effects which may occur include:

- If you have diabetes, this may not be as well controlled;
- Low blood pressure causing lack of concentration, light-headedness, headache, dizziness, drowsiness, weakness, dry mouth or problems with your eyesight;
- Itching, marks on the skin, flaky or scaly skin;
- Thirst, high blood pressure, confusion, muscle cramps, muscle weakness, irregular heart beat;
- Dehydration;
- Thrombosis in the elderly;
- If administered during the first weeks of life, in premature infants poor growth, shortness of breath and rapid breathing.

If you feel unwell in any other way, tell your doctor as soon as you can.

Storing your medicine

Keep Furosemide 20, 40 or 50mg/5ml Oral Solution in a safe place where children cannot see or reach it. Do not store above 25°C.

Store in the original package.

Protect from light

Once opened, use within 3 months.

Do not take the Furosemide 20, 40 or 50mg/5ml Oral Solution after the 'expiry' date printed on the label and the carton.

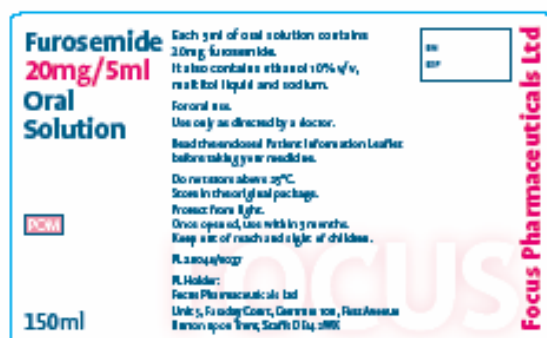
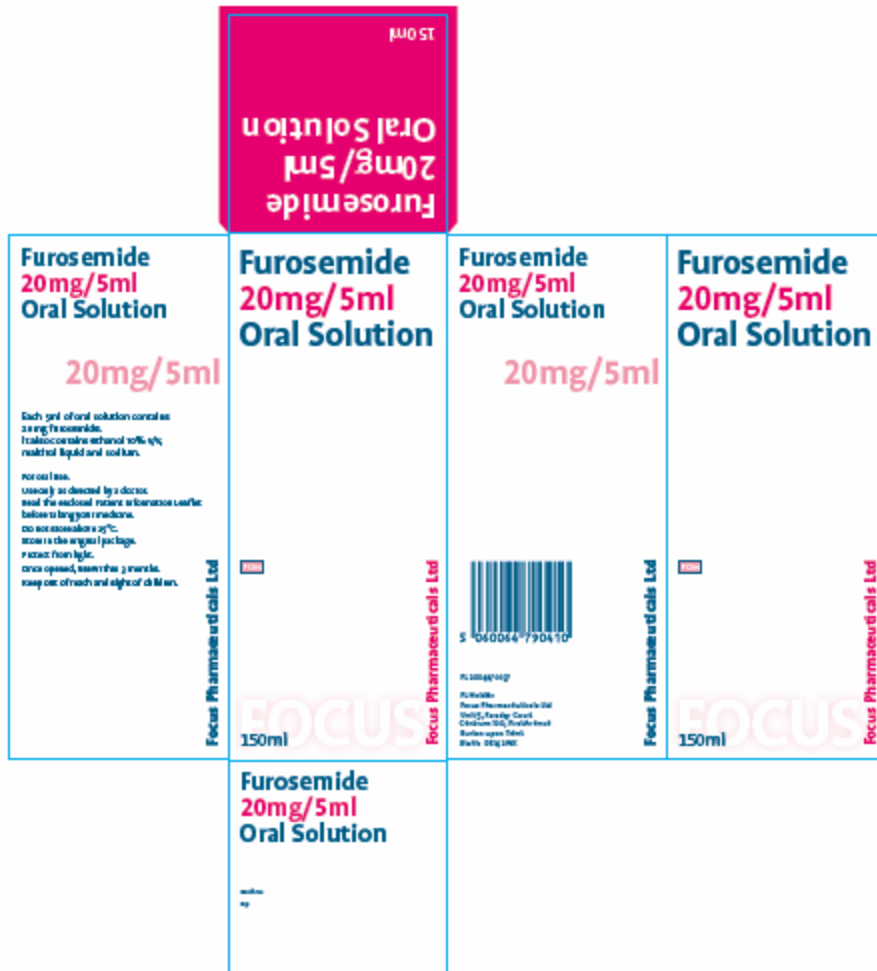
This leaflet was prepared in September 2005.

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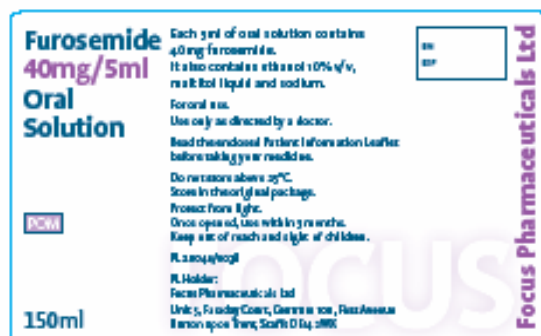
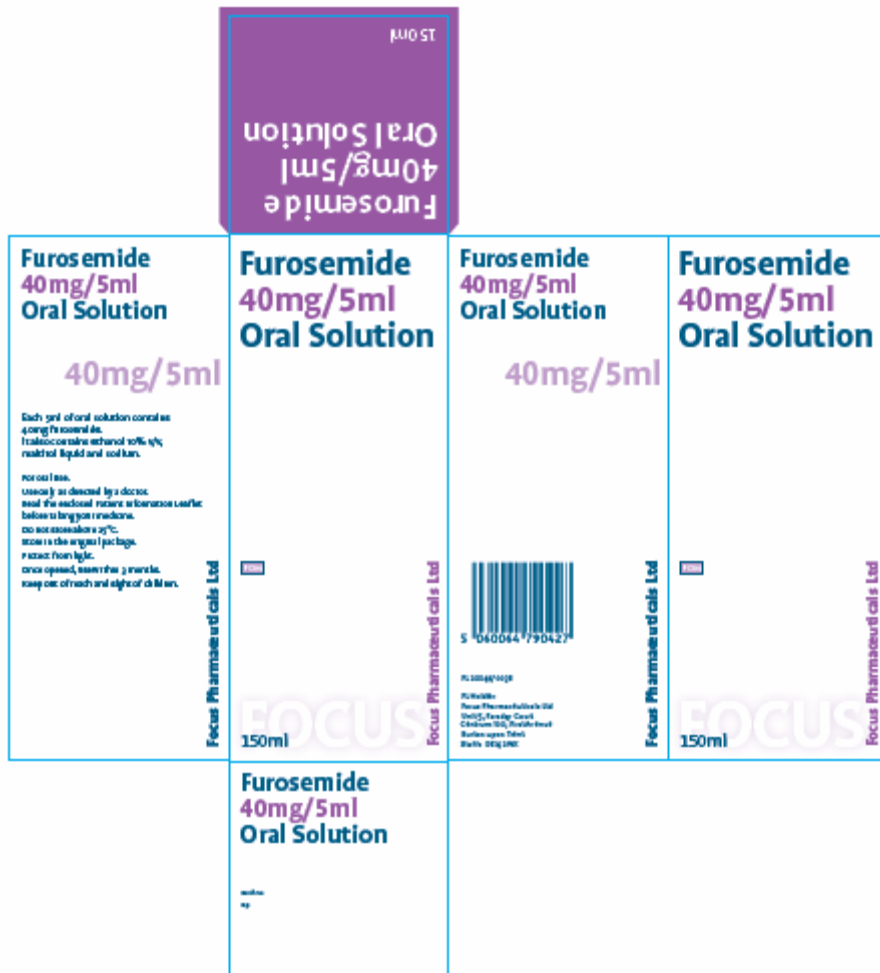
**FUROSEMIDE 20 MG/5 ML ORAL SOLUTION (FUROSEMIDE)
PL 20046/0037**

LABELLING



**FUROSEMIDE 40 MG/5 ML ORAL SOLUTION (FUROSEMIDE)
PL 20046/0038**

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