# FUROSEMIDE 20 MG/5 ML, 40 MG/5 ML AND 50 MG/5 ML ORAL SOLUTION

**PL 04917/0072-74**

**UKPAR**

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The Medicines and Healthcare products Regulatory Agency granted Pinewood Laboratories Ltd Marketing Authorisations (licences) for the medicinal products Furosemide 20 mg/5 ml, 40 mg/5 ml and 50 mg/5 ml Oral Solution (PL 04917/0072-74). These products are only available with a prescription.

Certain diseases can cause an excess of fluid in the body. Furosemide helps prevent this fluid build up by increasing the amount of urine produced by the kidneys. This particular product can be used in patients who are unable to take furosemide tablets.

Diurectics similar to Furosemide have been available in the European Union, including the UK, for more than ten years. Their use is well established, with recognised efficacy and acceptable safety.

Furosemide 20 mg/5 ml, 40 mg/5 ml and 50 mg/5 ml Oral Solution raised no clinically significant safety concerns and it was therefore judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.
FUROSEMIDE 20 MG/5 ML, 40 MG/5 ML AND 50 MG/5 ML ORAL SOLUTION

PL 04917/0072-74

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 20 mg/5 ml, 40 mg/5 ml and 50 mg/5 ml Oral Solution (PL 04917/0072-74) to Pinewood Laboratories Ltd on 3 July 2006. These oral solutions are prescription only medicines.

These are national applications for Furosemide 20 mg/5 ml, 40 mg/5 ml and 50 mg/5 ml Oral Solution, submitted under EC Article 10.1 of Directive 2001/83/EC. The applicant states that subsequent Mutual Recognition Procedures are considered.
PHARMACEUTICAL ASSESSMENT

I. REQUESTS FOR INSPECTION ACTION PRIOR TO AUTHORISATION

Not applicable.

II. 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 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 9 June 1993. The applicant also refers to the generic product Frusol (Rosemount) Oral Solution that has been granted marketing authorisations for the 20 mg/5 ml, 40 mg/5 ml and 50 mg/5 ml strengths (PL: 004270109-11) since 6 April 1998. 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, renal and peripheral oedema.

III. DRUG SUBSTANCE

III.1 General information

The active substance is described by a monograph of the Ph. Eur. and both the drug substance manufacturers have provided a Ph. Eur. certificate of suitability.

III.1.1 Nomenclature

Recommended International Nonproprietary Name (INN): Furosemide

Compendial Name: Furosemide

Chemical Name:
5-(aminosulfonyl)-4-chloro-2-[2-furanylmethyl]amino]benzoic acid;
4-chloro-N-furfuryl-5-sulfamoylanthranilic acid;
4-chloro-N-(2-furylmethyl)-5-sulfamoylanthranilic acid

III.1.2 Structure

![Chemical Structure]

\[ \text{C}_{12}\text{H}_{11}\text{ClN}_{2}\text{O}_{5} \]  
Mw: 330.7
III.1.3 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.

It melts at about 210°C, with decomposition.

III.2 Manufacture

III.2.1 Manufacturers

There are two manufacturers of the drug substance; both are suitable for manufacture of this drug substance and hold a Ph. Eur. certificate of suitability (CoS). Current Certificates of Suitability have been provided.

III.2.2 Description of Manufacturing Process and Process Controls

Covered by the CoS.

III.2.3 Control of Materials

Covered by the CoS.

III.2.4 Controls of Critical Steps and Intermediates

Covered by the CoS.

III.2.5 Process Validation and/or Evaluation

Covered by the CoS.

III.2.6 Manufacturing Process Development

Covered by the CoS.

III.3 Characterisation

III.3.1 Elucidation of Structure and other Characteristics

It is sometimes necessary to assess data relating to the physical characteristics (particle size, polymorphism) of the drug substance that are not controlled by the monograph but may influence the quality of the product. However, because the drug product is an oral solution, control of these parameters is unnecessary.

III.3.2 Impurities

Covered by the CoS.

III.4 Control of Drug Substance

III.4.1 Specification

The specification is in line with the Ph. Eur. monograph and the applicant states that the specification will be updated in line with each new edition of the Ph.Eur monograph for furosemide. This is acceptable.

III.4.2 Analytical Procedures

Covered by the CoS.
III.4.3 Validation of Analytical Procedures
Covered by the CoS.

III.4.4 Batch Analyses
Both drug substance manufacturers have provided batch analytical data for six production scale batches, which conform to Ph. Eur. requirements.

III.4.5 Justification of Specification
Not applicable

III.5 Reference Standards or Materials
Covered by the CoS.

III.6 Container Closure System
Satisfactory details of the packaging materials from both drug substance manufacturers have been provided. Suitability is further confirmed by the stability data.

III.7 Stability

III.7.1 Stability Summary and Conclusions
Forty-eight month’s long term (25 °C/60 % RH) stability data have been provided for six batches from one drug substance manufacturer. Sixty month’s long term (25 °C/60 % RH) and 6 month’s accelerated (40 °C/75 % RH) stability data have been provided for three batches from the second supplier.

If there is greater than 12 month’s expiry remaining on the supplier certificate of analysis (COA), an expiry date of 12 months from test date in Pinewood Healthcare is applied. After this, the material can be retested on one or more occasions and given a further 6 months expiry on each occasion provided this does not exceed the supplier expiry date and complies with the specifications. The COA’s indicate a 5 year expiry date with the storage conditions ‘protect from light.’ The drug safety datasheet further indicates that storage is undertaken in refrigerated conditions. This is supported by stability data.

III.7.2 Post-Approval Stability Protocol and Stability Commitment
Since the dossier includes long-term stability data on at least three production batches covering the proposed re-test period, a post approval commitment is considered unnecessary.

III.7.3 Stability Data
Stability data for the six batches from one supplier demonstrates their drug substance is stable at 25 °C/60 % RH. Assay levels remain constant and there is no apparent trend for increasing levels of impurities. Stability data for the three batches from the second supplier demonstrate their drug substance is very stable. All data is acceptable.

IV. DRUG PRODUCT

IV.1 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
Qualitative composition of Furosemide 20 mg/5 ml, 40 mg/5 ml and 50 mg/5 ml Oral Solution

<table>
<thead>
<tr>
<th>Active Components</th>
<th>Function</th>
<th>Quality standard</th>
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<tr>
<td>1 Furosemide</td>
<td></td>
<td>Ph.Eur</td>
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<tr>
<th>Excipients</th>
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<tbody>
<tr>
<td>2 Liquid maltitol</td>
<td>Vehicle/Sweetener</td>
<td>Ph.Eur</td>
</tr>
<tr>
<td>3 Ethanol (96%)</td>
<td>Preservative</td>
<td>Ph.Eur</td>
</tr>
<tr>
<td>4 Disodium hydrogen phosphate dodecahydrate</td>
<td>Buffer</td>
<td>Ph.Eur</td>
</tr>
<tr>
<td>5 Sodium hydroxide</td>
<td>pH adjuster/Active solubiliser</td>
<td>Ph.Eur</td>
</tr>
<tr>
<td>6 Citric acid monohydrate</td>
<td>Buffer</td>
<td>Ph.Eur</td>
</tr>
<tr>
<td>7 Flavour cherry</td>
<td>Flavour</td>
<td>HSE</td>
</tr>
<tr>
<td>8 Quinoline yellow E104 (for 20mg/5ml product only)</td>
<td>Colour</td>
<td>HSE</td>
</tr>
<tr>
<td>9 Purified water</td>
<td>Vehicle and solvent</td>
<td>Ph.Eur</td>
</tr>
</tbody>
</table>

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

IV.2 Pharmaceutical Development

IV.2.1 Components of the Drug product

The qualitative composition of all three strengths is similar, with the exception of the quinoline yellow colouring in the 20 mg/5 ml strength.

The applicant states that the formulation is qualitatively identical to a ‘reference’ product, Frusol (Rosemount).

IV.2.1.1 Drug Substance

The applicant refers to the qualitative similarity of the reference product 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.

The drug substance is supplied in compliance with the Ph. Eur. monograph. Further control of physical characteristics is unnecessary since the product is a solution. The dissolution of the drug substance is ensured by controlling the pH of the solution. The absence of precipitation has been demonstrated in stability studies.

IV.2.1.2 Excipients
A brief description of the excipients and their intended use is provided. All are common to oral solutions. Ethanol is included to function as an antimicrobial preservative.

IV.2.2 Drug Product

IV.2.2.1 Formulation development
This was focused on formulating a product essentially similar to Frusol 20 mg/5 ml, 40 mg/5 ml and 50 mg/5 ml oral solutions (market leader in the UK).

IV.2.2.2 Overages
None added.

IV.2.2.3 Physicochemical and biological properties
Not applicable.

IV.2.3 Manufacturing Process Development
The manufacturing process is very straightforward. A brief description is provided.

IV.2.4 Container Closure System
The primary packaging is common for this type of product. Refer to section IV.7.

IV.2.5 Microbiological Attributes
Analytical testing of several batches of the finished product with 100 % and 90 % preservative was performed against the Ph. Eur. test for efficacy of antimicrobial preservation. The recommended efficacy against bacteria ($10^3$ log reduction) and fungi ($10^1$ log reduction) was demonstrated. This is acceptable.

IV.2.6 Compatibility
There are not considered to be compatibility issues with this product.

IV.3 Manufacture

IV.3.1 Manufacture(s)
The drug product is manufactured at a suitable site.

IV.3.2 Batch Formula
The batch formula for each strength is presented for the manufacturing batches.

IV.3.3 Description of Manufacturing Process and Process Controls
A flow diagram and full description of the synthetic process and process controls has been provided. This information is satisfactory.

IV.3.4 Control of Critical Steps and Intermediates
No intermediates are generated and critical steps are controlled with suitable in-process controls, including visual inspection for dissolution and pH limit tests. This is acceptable.

IV.3.5 Process Validation and/or Evaluation
Process validation was performed for the manufacture of two batches for all three strengths of the product.
Testing performed is minimal and involves the analysis of samples, taken from the top, middle and bottom of the manufacturing vessel, to the finished product specifications following final mixing. Given the simplicity of the process this is acceptable. Data are supportive.

The applicant states that batch sizes are typically scaled up by a factor of 10 and the process re-validated. Acceptable manufacturing batch sizes are proposed and the applicant commits to notifying the regulatory authority of any significant deviations in scale-up; a signed letter of commitment has been provided together with a process validation protocol for production scale batches.

IV.4 Control of Excipients

IV.4.1 Specifications

Most of the excipients used are controlled according to their respective Ph. Eur. monographs. Certificates of analysis are checked to ensure compliance and minimum QC testing for description, identity and assay are performed on each batch. This is acceptable.

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 cherry flavouring and Quinoline Yellow comply with EC purity requirements is provided.

IV.4.2 Analytical Procedures

Where applicable a brief description of the analytical testing is provided. This is acceptable.

IV.4.3 Validation of Analytical Procedure

- 

IV.4.4 Justification of Specification

- 

IV.4.5 Excipients of Human or Animal Origin

None.

IV.4.6 Novel Excipients

Not applicable.

IV.5 Control of Drug Product

IV.5.1 Specification(s)

The finished product specifications are acceptable for a product of this type.

IV.5.2 Analytical Procedures

Details of the analytical testing methods have been provided and are acceptable. The HPLC methods for determination of assay and related substances are different. The HPLC method for related substances is very similar (same chromatographic conditions) as the method described in the Ph. Eur. monograph for Furosemide.
Details of the method used to determine microbial contamination have been provided and are satisfactory.

IV.5.3 Validation of Analytical Procedures

The assay HPLC method has been adequately validated. The linearity of the method has been demonstrated over a range encompassing the 100% nominal concentration for all three strengths. The data and subsequent demonstration of accuracy and precision confirm the suitability of the method. System suitability, sensitivity and robustness and sample solution stability have also been demonstrated. The stability indicating nature of the method has also been demonstrated through forced degradation studies. This is acceptable.

Even though the HPLC method for related substances is similar to that described in the Ph. Eur. monograph, a full validation has been performed. The method is shown to be specific, sensitive and stability indicating.

The GC method for the determination of ethanol has also been suitably validated.

IV.5.4 Batch Analyses

Batch analytical data refers to the process validation samples taken at the end of the manufacture of the two pilot scale batches of each strength and presumably, prior to packaging. However, since the filling process is unlikely to affect product quality and the samples were tested according to the full finished product specification, this is acceptable. Furthermore, the quality of the product in the final packaging can be inferred from the stability data.

IV.5.5 Characterisation of Impurities

The impurities identified are those listed in the Ph. Eur. monograph for the drug substance.

IV.5.6 Justification of Specification(s)

The specifications are suitable for a product of this type. Limits for the preservative are based on the results of preservative efficacy testing. Impurities are in line with the Ph. Eur. limits for the drug substance itself. This is acceptable.

IV.6 Reference Standards or Materials

A brief description of the source and testing of the reference standards is provided. Certificates of analysis for all reference standards used during analytical testing have been provided.

IV.7 Container Closure System

Bottle: Type III amber glass bottle.
Closure: Polypropylene child resistant closure with LDPE liner.

Specifications and confirmation of the compliance of the packaging with appropriate EU current standards have been provided. This is acceptable.

IV.8 Stability

IV.8.1 Stability Summary and Conclusion

Stability data for the following is enclosed:
1. Two batches of Furosemide 20mg/5ml oral solution:
2. Two batches of Furosemide 40mg/5ml oral solution:

3. Two batches of Furosemide 50mg/5ml oral solution:

The only difference between these batches, besides the strength of the active material, is that the 20mg/5ml formulation also contains a colouring agent. The formulations also contain a sodium hydroxide buffer which is used to control the pH and this will change from batch to batch. No overages were used in the stability batches. The formulations of the stability batches are as outlined in 3.2.P.3.2. These are the same batches that the process validation was carried out on.

The final product placed on stability and intended for marketing is a 150 type III amber glass bottle, with a polypropylene child resistant closure with LDPE liner. The studies were performed in accordance with ICH guidelines.

IV.8.2 Post-approval Stability Protocol and Stability Commitment

A post-approval stability protocol has been provided. The protocol includes preservative efficacy testing that will be performed (in addition to preservative content) on the primary production batches. The applicant has confirmed that testing will be performed on the first three production scale batches.

IV.8.3 Stability Data

The applicant has provided updated long-term stability data (24 months), 90 day in-use stability data and details of preservative efficacy testing performed during in-use stability testing.

The stability data provided support a shelf-life of 18 months (do not store above 25 °C). For all batches under all conditions there is no indication of precipitation by visual description (even at 5 °C) and pH and ethanol levels remain constant.

Microbial contamination testing will be performed at 12 months (all conditions), 24 and 36 months (long-term).

The stability studies will continue up to 36 months.

V. APPENDICES

V.1 Facilities and Equipment

Not applicable.

V.2 Adventitious Agents Safety Evaluation

Not applicable

V.3 Novel Excipients

Not applicable
VI. REGIONAL INFORMATION
Not applicable.

VII. ASSESSOR’S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET
All SPCs, labels and packaging is satisfactory.

VII.1 Other information
Not applicable.

VII.1.2 Bio-analytical methods
Not applicable.

VII.1.3 Bioavailability, bioequivalence
Not applicable.

VII.1.4 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. The application also refers to Frusol 20 mg/5 ml, 40 mg/5 ml and 50 mg/5 ml Oral Solution which was granted a licence on the basis of an abridged application to the 20 mg Lasix tablets and is qualitatively identical to the test product.

VII.2.1 Administrative

VII.2.2 Comment on Expert report
A detailed expert report has been provided, addressing the critical points related to the quality of the medicinal product.

VII.2.3 MAA form
The MAA form is satisfactory.

VII.2.4 GMP
Suitable manufacturing authorisations have been provided to ensure the product is manufactured according to the principles of GMP.

VII.2.5 Guideline Compliance
In general, the dossier is in line with current guidelines.

VIII. ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY AND ADVICE
In general the dossier is well presented. Granting of a marketing authorisation is recommended.
PRECLINICAL ASSESSMENT

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

1. INTRODUCTION
This is a generic application for furosemide oral solution. The original product is Lasix 10mg/ml liquid (PL number 00086/0142, became PL 13402/0019). The marketing authorisation granted to Hoechst UK on 9 June 1993 was transferred to Hoechst Marion Roussel on 1 November 1997 (PL 13402/0019).

2. BACKGROUND
ATC code C03CA01 High Ceiling Diuretics – Sulfonamides Plain

3. INDICATIONS
“Furosemide is indicated in all conditions requiring prompt diuresis, including cardiac, pulmonary, hepatic and renal oedema, peripheral oedema due to mechanical obstruction or venous insufficiency and hypertension.

It is also indicated for the maintenance therapy of mild oedema of any origin.”

4. DOSE & DOSE SCHEDULE
“This liquid should only be taken orally.

The medication should be administered in the morning to avoid nocturnal diuresis.

Adults: The usual initial daily dose is 40 mg. This may be adjusted until an effective dose is achieved.

Children: 1 to 3 mg/Kg body weight daily up to a maximum total dose of 40 mg/day.

Elderly: In the elderly, Furosemide is generally eliminated more slowly. Dosage should be titrated until the required response is achieved.”

5. TOXICOLOGY
The 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. The 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 overview was written by a consultant pharmaceutical physician. The report has reviewed safety and efficacy of furosemide.

10. **SUMMARY OF PRODUCT CHARACTERISTICS**
The SPC is in line with the SPC of the original product Lasix 10mg/ml liquid (PL 13402/0019) and is satisfactory.

11. **PATIENT INFORMATION LEAFLET**
Patient information leaflet will need to be amended in line with the final agreed SPC.

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.

14. **CONCLUSIONS**
A marketing authorisation is recommended.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Furosemide 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
The indication is for all conditions requiring prompt diuresis, including cardiac, pulmonary, hepatic and renal oedema, peripheral oedema due to mechanical obstruction or venous insufficiency and hypertension. Furosemide is also indicated for the maintenance therapy of mild oedema of any origin.”

The efficacy of Furosemide was demonstrated in all clinical studies presented.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no significant preclinical or clinical safety concerns were identified. When used as indicated, Furosemide Oral Solution has a favourable benefit-to-risk ratio. The hazard associated with Furosemide Oral Solution appears to be low and acceptable when considered in relation to its therapeutic benefits.
**FUROSEMIDE 20 MG/5 ML, 40 MG/5 ML AND 50 MG/5 ML ORAL SOLUTION**

**PL 04917/0072-74**

**STEPS TAKEN FOR ASSESSMENT**

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<td>1</td>
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<tr>
<td>2</td>
<td>Following assessment of the application the MHRA requested further information relating to the quality dossier on 9 March 2005 and relating to the clinical dossier on 7 April 2005</td>
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<tr>
<td>3</td>
<td>The applicant responded to the MHRA’s request, providing further information on the quality dossier on 24 June 2005 and on the clinical dossier on 3 June 2005</td>
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<tr>
<td>4</td>
<td>Following assessment of the applicant’s response the MHRA requested further information relating to the quality dossier on 16 August 2005 and the clinical dossier on 30 August 2005</td>
</tr>
<tr>
<td>5</td>
<td>The applicant responded to the MHRA’s request, providing further information on the quality dossier on 29 November 2005 and the clinical dossier on 12 September 2005</td>
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<td>6</td>
<td>Following assessment of the applicant’s response the MHRA requested further information relating to the quality dossier on 20 December 2005</td>
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<tr>
<td>7</td>
<td>The applicant responded to the MHRA’s request, providing further information on the quality dossier on 21 February 2006</td>
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<td>8</td>
<td>Following assessment of the applicant’s response the MHRA requested further information relating to the quality dossier on 1 March 2006</td>
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<tr>
<td>9</td>
<td>The applicant responded to the MHRA’s request, providing further information on the quality dossier on 30 June 2006</td>
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<tr>
<td>10</td>
<td>The application was determined on 3 July 2006</td>
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SUMMARY OF PRODUCT CHARACTERISTICS

Furosemide 20 mg/5 ml Oral Solution (PL 04917/0072) has the following product summary:

1. NAME OF THE MEDICINAL PRODUCT

   Furosemide 20 mg/5 ml Oral Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

   Each 5ml contains Furosemide 20 mg.

   For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

   Oral Solution
   Clear, yellow, cherry flavoured, oral solution

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

   Furosemide oral solution is indicated in all conditions requiring prompt diuresis 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 and hypertension.

4.2 Posology and method of administration

   Furosemide 20mg/5ml has an exceptionally wide therapeutic range, the effect being proportional to the dosage. Furosemide 20mg/5ml 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 80mg and above may be used as one or two dose 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 1500mg.

   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 Contraindications

Furosemide 20mg/5ml is contraindicated 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/5ml. 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.
- 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 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 product contains liquid maltitol. Patients with a rare hereditary problem of fructose intolerance should not take this medicine.

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 3 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.

Oral furosemide and sucralfate must not be taken within 2 hours of each other because sucralfate decreases the absorption of furosemide from the intestine and so reduces its effect.

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 amines) and sometimes potentiate them (e.g. the effects of salicylates, theophylline and curare-form 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. 40mg 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 effects 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, 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.

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 being treated with furosemide.

4.7 Effects on ability to drive and use machines

Mental alertness may be reduced and the ability to drive or operate machinery may be impaired.

4.8 Undesirable effects

Furosemide 20mg/5ml 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 nephritic 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 they 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 designated to reduce absorption (e.g. activated charcoal).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

High ceiling Diuretic Sulfonamide – CO3C 1 01

Furosemide is a potent loop diuretic which inhibits sodium and chloride reabsorption at the Loop of Henlé. Furosemide acts at the luminal face of the epithelial cells by inhibiting co-transport mechanisms for the entry of sodium and chloride. Furosemide gains access to its site of action by being transported through the secretory pathway for organic acids in the proximal tubule. It reduces the renal excretion of uric acid. Furosemide causes an increased loss of potassium in the urine and also increases the excretion of ammonia by the kidney.

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. In plasma, furosemide is extensively bound to proteins mainly albumin. The unbound fraction in plasma averages 2 – 4% at therapeutic concentrations. The volume of distribution ranges between 170 – 270 ml/Kg. The half life of the β phase ranges from 45 – 60 min.

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 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 excipient(s)
Ethanol, sodium hydroxide, quinoline yellow E104, cherry flavour (containing propylene glycol), liquid maltitol, disodium hydrogen phosphate, citric acid monohydrate and purified water.

6.2 Incompatibilities
None known

6.3 Shelf-life
18 months
3 months once opened

6.4 Special precautions for storage
Do not store above 25°C.

6.5 Nature and contents of container
Bottles: Amber (Type III) glass
Closures:
Polypropylene Child Resistant Closures (CRCs) with LDPE liners
Capacity: 150 ml

6.6 Instructions for use and handling
Not applicable.
Furosemide 40 mg/5 ml Oral Solution (PL 04917/0073) has the following product summary:

1. NAME OF THE MEDICINAL PRODUCT
   Furosemide 40 mg/5 ml Oral Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
   Each 5ml contains Furosemide 40 mg.
   For excipients, see section 6.1.

3. PHARMACEUTICAL FORM
4. **CLINICAL PARTICULARS**

4.1 **Therapeutic Indications**

Furosemide oral solution is indicated in all conditions requiring prompt diuresis 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 and hypertension.

4.2 **Posology and method of administration**

Furosemide 40mg/5ml has an exceptionally wide therapeutic range, the effect being proportional to the dosage. Furosemide 40mg/5ml 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 80mg and above may be used as one or two dose 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 1500mg.

*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 **Contraindications**

Furosemide 40mg/5ml is contraindicated 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 40mg/5ml. 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.
- 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 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 product contains liquid maltitol. Patients with a rare hereditary problem of fructose intolerance should not take this medicine.

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 3 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.

Oral furosemide and sucralfate must not be taken within 2 hours of each other because sucralfate decreases the absorption of furosemide from the intestine and so reduces its effect.

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 amines) and sometimes potentiate them (e.g. the effects of salicylates, theophylline and curare-form 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. 40mg 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 effects 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, 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.

### 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 being treated with furosemide.

4.7 Effects on ability to drive and use machines

Mental alertness may be reduced and the ability to drive or operate machinery may be impaired.

4.8 Undesirable effects

Furosemide 40mg/5ml 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 nephritic 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 they 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 designated to reduce absorption (e.g. activated charcoal).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

High ceiling Diuretic Sulfonamide – CO3C 1 01

Furosemide is a potent loop diuretic which inhibits sodium and chloride reabsorption at the Loop of Henlé. Furosemide acts at the luminal face of the epithelial cells by inhibiting co-transport mechanisms for the entry of sodium and chloride. Furosemide gains access to its site of action by being transported through the secretory pathway for organic acids in the proximal tubule. It reduces the renal excretion of uric acid. Furosemide causes an increased loss of potassium in the urine and also increases the excretion of ammonia by the kidney.

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. In plasma, furosemide is extensively bound to proteins mainly albumin. The unbound fraction in plasma averages 2 – 4% at therapeutic concentrations. The volume of distribution ranges between 170 – 270 ml/Kg. The half life of the β phase ranges from 45 – 60 min.

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 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 excipient(s)
Ethanol, sodium hydroxide, cherry flavour (containing propylene glycol), liquid maltitol, disodium hydrogen phosphate, citric acid monohydrate and purified water.

6.2 **Incompatibilities**

None known

6.3 **Shelf-life**

18 months

3 months once opened

6.4 **Special precautions for storage**

Do not store above 25°C.

6.5 **Nature and contents of container**

Bottles: Amber (Type III) glass

Closures:

Polypropylene Child Resistant Closures (CRCs) with LDPE liners

Capacity: 150 ml

6.6 **Instructions for use and handling**

Not applicable.

7. **MARKETING AUTHORISATION HOLDER**

Pinewood Laboratories Limited
Ballymacarbry
Clonmel
Co. Tipperary
Ireland
Furosemide 50 mg/5 ml Oral Solution (PL 04917/0074) has the following product summary:

1. **NAME OF THE MEDICINAL PRODUCT**
   Furosemide 50 mg/5 ml Oral Solution

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**
   Each 5ml contains Furosemide 50 mg.
   For excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**
   Oral Solution
   Clear, cherry flavoured, oral solution.

4. **CLINICAL PARTICULARS**
   4.1 **Therapeutic Indications**
   Furosemide oral solution is indicated in all conditions requiring prompt diuresis 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 and hypertension.
4.2 Posology and method of administration

Furosemide 50mg/5ml has an exceptionally wide therapeutic range, the effect being proportional to the dosage. Furosemide 50mg/5ml 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 80mg and above may be used as one or two dose 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 1500mg.

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 Contraindications

Furosemide 50mg/5ml is contraindicated 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. 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.
- 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 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 product contains liquid maltitol. Patients with a rare hereditary problem of fructose intolerance should not take this medicine.

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 3 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.

Oral furosemide and sucralfate must not be taken within 2 hours of each other because sucralfate decreases the absorption of furosemide from the intestine and so reduces its effect.

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 amines) and sometimes potentiate them (e.g. the effects of salicylates, theophylline and curare-form 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. 40mg 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 effects 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, 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.

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 being treated with furosemide.

4.7 Effects on ability to drive and use machines

Mental alertness may be reduced and the ability to drive or operate machinery may be impaired.

4.8 Undesirable effects
Furosemide 50mg/5ml 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 nephritic 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 they 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 designated to reduce absorption (e.g. activated charcoal).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Furosemide is a potent loop diuretic which inhibits sodium and chloride reabsorption at the Loop of Henlé. Furosemide acts at the luminal face of the epithelial cells by inhibiting co-transport mechanisms for the entry of sodium and chloride. Furosemide gains access to its site of action by being transported through the secretory pathway for organic acids in the proximal tubule. It reduces the renal excretion of uric acid. Furosemide causes an increased loss of potassium in the urine and also increases the excretion of ammonia by the kidney.

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. In plasma, furosemide is extensively bound to proteins mainly albumin. The unbound fraction in plasma averages 2 – 4% at therapeutic concentrations. The volume of distribution ranges between 170 – 270 ml/Kg. The half life of the β phase ranges from 45 – 60 min.

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 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 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. In plasma, furosemide is extensively bound to proteins mainly albumin. The unbound fraction in plasma averages 2 – 4% at therapeutic concentrations. The volume of distribution ranges between 170 – 270 ml/Kg. The half life of the β phase ranges from 45 – 60 min.

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 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 excipient(s)

Ethanol, sodium hydroxide, cherry flavour (containing propylene glycol), liquid maltitol, disodium hydrogen phosphate, citric acid monohydrate and purified water.

6.2 Incompatibilities

None known

6.3 Shelf-life

18 months

3 months once opened
6.4 **Special precautions for storage**

Do not store above 25°C.

6.5 **Nature and contents of container**

Bottles: Amber (Type III) glass

Closures:

Polypropylene Child Resistant Closures (CRCs) with LDPE liners

Capacity: 150 ml

6.6 **Instructions for use and handling**

Not applicable.

7. **MARKETING AUTHORISATION HOLDER**

Pinewood Laboratories Limited
Ballymacarbry
Clonmel
Co. Tipperary
Ireland

8. **MARKETING AUTHORISATION NUMBER(S)**

PL 04917/0074

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

03/07/2006

10. **DATE OF REVISION OF THE TEXT**

03/07/2006
PATIENT INFORMATION LEAFLET

Patient Information Leaflet
Furosemide 20 mg/5 ml Oral Solution

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:
1. What Furosemide is and what it is used for.
2. Before you take Furosemide.
3. Possible side effects.
4. Storing Furosemide.
5. Further information.

The active substance is Furosemide. The other ingredients are liquid maltitol, ethanol 96%, disodium hydrogen phosphate dodecahydrate, sodium hydroxide, citric acid monohydrate, flavour cherry (containing propylene glycol), quinoline yellow (E104) and purified water.

Furosemide 20 mg/5 ml is available in 150 ml amber glass bottles.

Marketing Authorisation Holder and Manufacturer:
Pinewood Laboratories Limited trading as Pinewood Healthcare, Ballymacarbry, Clonmel, Co. Tipperary, Ireland. PL 04917/0072

1. What Furosemide is and what it is used for;
Furosemide is an oral solution which contains 20 mg Furosemide in each 5 ml. Certain conditions which affect the heart, lungs, kidney, liver or blood vessels can lead to build up of water in the body. Furosemide belongs to a group of medicines called Diuretics which are used to reduce excess amounts of water in the body.

2. Before you take Furosemide:
Do not take Furosemide without first informing your doctor if you:
- ever had a bad reaction (hypersensitivity) to furosemide, sulphonamides or any of the ingredients listed.
- have liver problems particularly cirrhosis.
- have kidney problems.
- are pregnant or breast-feeding.
- have enlargement of the prostate gland.
- have low blood pressure, low blood salts or low blood volume.
- are diabetic.
- have gout.

Take special care with Furosemide if:
- urine flow is partly obstructed. This could lead to fluid retention.
- you have low blood pressure (hypotension).
- you are at risk from a sharp fall in blood pressure.
- you have diabetes or are pre-disposed to diabetes.
- you are taking other medicines at the same time. See the section ‘Taking other medicines’ for more information.

The doctor may take blood samples in order to monitor how Furosemide is working while you are taking this medication.

Pregnancy and Breast-feeding:
Furosemide should be used with caution during pregnancy and whilst breast-feeding. Only to be used if strictly necessary.

Driving and using machines:
Mental alertness may be reduced and ability to drive or operate machinery may be impaired.

Important information about some of the ingredients of Furosemide:
Ethanol:
This medicinal product contains 10 vol % ethanol (alcohol), i.e., up to 442 mg of ethanol per 5 ml dose, equivalent to 8 ml of beer or 3 ml of wine per dose. Harmful for those suffering from alcoholism.
To be taken into account in pregnant or breast-feeding women such as patients with liver disease or epilepsy.

Liquid Maltitol: If you have been told by your doctor that you have an Intolerance to some sugars, contact your doctor before taking this medicinal product.

3LF
Taking other medicines:  
Inform your doctor if you are taking any of the following medicines: Antibiotics, Lithium, ACE inhibitors (heart medication), medication for high and low blood pressure, non steroidal anti-inflammatory drugs (e.g. indomethacin, aspirin), muscle relaxants, salicylates, theophylline, glucocorticoids (prednisolone, dexamethasone), digoxin, cisplatin, succinylated, phenyltoin, carbamazepine, aminoglutethimide, carbamoxolone, liquorice, B2 sympathomimetics (used to raise blood pressure), probenecid, methotrexate, anti-diabetic medication and laxatives.

The dosage of some of your other medicines may need to be altered while using Furosemide as they may alter the effect of Furosemide. Your doctor will inform you of any changes required.

Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicines - even those received without a prescription.

3. How to take Furosemide:  
For oral administration only (to be taken via the mouth). Use as directed by your doctor. Do not exceed the stated dose. It is best to take this medicine in the morning, or according to a schedule that will least affect your personal activities and sleep. Ask your doctor or pharmacist for advice on when best to take this medicine.

Adults:  
The usual dose is 40 mg daily. This may need to be adjusted in order to determine the correct dose for you. Take exactly what is prescribed for you by your doctor.

Children:  
Children's doses may be lower (1 to 3 mg/kg body weight) but they must not take more than 40 mg a day.

Elderly:  
Dosage is generally titrated until the required response is achieved as furosemide is generally eliminated more slowly from the body.

Continue taking this medicine until your doctor tells you to stop.

If you take more Furosemide than you should:  
You should contact a doctor or hospital immediately.

If you forget to take Furosemide:  
Take the next dose as soon as you remember then continue taking as normal the following morning.

4. Possible side effects:  
Along with the desired effects, a medicine can also have some unwanted effects. Side effects are generally minor and furosemide is well tolerated. Although not all these side effects may occur, if they do then you may need medical attention. Nausea, tiredness, stomach upset (vomiting and diarrhoea), low blood pressure which may show as changes in concentration and reactions, light - headedness, sensation of pressure in the head, headache, drowsiness, dizziness, dizziness when standing, weakness, changes to vision and dry mouth), hearing loss, ringing in the ears, inflammation of the pancreas, kidney or blood vessels, itching, urticaria and cold. Furosemide may occasionally cause changes in the blood and your doctor may want to perform blood tests. If you are diabetic, Furosemide may interfere with your anti-diabetic medication.

Bone marrow depression and paraesthesiae can occur rarely. Tetany can occur very rarely.

Serum cholesterol and triglyceride levels may rise during Furosemide treatment. During long term treatment, these will usually return to normal within six months.

Allergic reactions, including skin rashes, increased sensitivity to light, inflammation of the blood vessels, fever and shock occur rarely. If they occur, Furosemide therapy should be stopped.

Due to the fluid loss during the use of Furosemide, the electrolyte and water balance in the body might be disturbed. You might observe an increased thirst, headache, a fall in blood pressure, confusion, muscle cramps, muscle weakness and stomach upset.

Changes in blood volume and dehydration due to loss of fluid may occur, particularly in elderly patients.

Aggravation of conditions in patients with obstructions to urinary flow might occur due to the extra fluid volumes excreted when using Furosemide.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. Storing Furosemide:  
Do not store above 25° C. Once the bottle has been opened for more than 3 months it should not be used. Keep out of the reach of children.

6. Further information:  
Do not use after the expiry date printed on the label. Do not keep outdated medicine, or medicine that is no longer wanted. Take it to your pharmacist for safe disposal. Always keep the medicine in the bottle in which it was given to you by your pharmacist.

This leaflet was last approved in June 2005.
Patient Information Leaflet
Furosemide 40 mg/5 ml Oral Solution

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:
1. What Furosemide is and what it is used for.
2. Before you take Furosemide.
3. How to take Furosemide.
4. Possible side effects.
5. Storing Furosemide.
6. Further information.

The active substance is Furosemide. The other ingredients are liquid maltitol, ethanol 96%, disodium hydrogen phosphate dodecahydrate, sodium hydroxide, citric acid monohydrate, flavour cherry (containing propylene glycol) and purified water.

Furosemide 40 mg/5 ml is available in 150 ml amber glass bottles.

Marketing Authorisation Holder and Manufacturer:
Pinewood Laboratories Limited trading as Pinewood Healthcare, Ballymacarbery, Clonmel, Co. Tipperary, Ireland. PL 04917/0073

1. What Furosemide is and what it is used for:
Furosemide is an oral solution which contains 40 mg Furosemide in each 5 ml. Certain conditions which affect the heart, lungs, kidney, liver or blood vessels can lead to build up of water in the body. Furosemide belongs to a group of medicines called Diuretics which are used to reduce excess amounts of water in the body.

2. Before you take Furosemide:
Do not take Furosemide without first informing your doctor if you:
- ever had a bad reaction (hypersensitivity) to furosemide, sulphonamides or any of the ingredients listed.
- have liver problems particularly cirrhosis.
- have kidney problems.
- are pregnant or breast-feeding.
- have enlargement of the prostate gland.
- have low blood pressure, low blood salts or low blood volume.
- are diabetic.
- have gout.

Take special care with Furosemide if:
- urinary flow is partly obstructed. This could lead to fluid retention.
- you have low blood pressure (hypotension).
- you are at risk from a sharp fall in blood pressure.
- you have diabetes or are pre-disposed to diabetes.
- you are taking other medicines at the same time. See the section ‘Taking other medicines’ for more information.

The doctor may take blood samples in order to monitor how Furosemide is working while you are taking this medication.

Pregnancy and Breast-feeding:
Furosemide should be used with caution during pregnancy and whilst breast-feeding. Only to be used if strictly necessary.

Driving and using machines:
Mental alertness may be reduced and ability to drive or operate machinery may be impaired.

Important Information about some of the ingredients of Furosemide:
Ethanol
This medicinal product contains 10 vol % ethanol (alcohol), i.e., up to 442 mg of ethanol per 5 ml dose, equivalent to 8 ml of beer or 3 ml of wine per dose.
Harmful for 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.

Liquid Maltitol: If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product. 3LF
Taking other medicines:
Inform your doctor if you are taking any of the following medicines:
Antibiotics, Lithium, ACE inhibitors (heart medication), medication for high and low blood pressure, non steroidal anti-inflammatory drugs (e.g. indomethacin, aspirin), muscle relaxants, salicylates, theophylline, glucocorticoids (prednisolone, dexamethasone), digoxin, captopril, sucralfate, phenytoin, carbamazepine, amitriptyline, carbamazepine, liquorice, B2 sympathomimetics (used to raise blood pressure),probenecid, methotrexate, anti-diabetic medication and laxatives.

The dosage of some of your other medicines may need to be altered while using Furosemide. Your doctor will inform you of any changes required.

Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicines - even those received without a prescription.

3. How to take Furosemide:
For oral administration only (to be taken via the mouth). Use as directed by your doctor. Do not exceed the stated dose. It is best to take this medicine in the morning, or according to a schedule that will least affect your personal activities and sleep. Ask your doctor or pharmacist for advice on when best to take this medicine.

Adults:
The usual dose is 40 mg daily. This may need to be adjusted in order to determine the correct dose for you. Take exactly as prescribed for you by your doctor.

Children:
Children's doses may be lower (1 to 3 mg/kg body weight) but they must not take more than 40 mg a day.

Elderly:
Dosage is generally titrated until the required response is achieved as furosemide is generally eliminated more slowly from the body.

Continue taking this medicine until your doctor tells you to stop.

If you take more Furosemide than you should:
You should contact a doctor or hospital immediately.

If you forget to take Furosemide:
Take the next dose as soon as you remember then continue taking as normal the following morning.

4. Possible side effects:
Along with the desired effects, a medicine can also have some unwanted effects. Side effects are generally minor and furosemide is well tolerated. Although not all these side effects may occur, if they do then you may need medical attention. Nausea, tiredness, stomach upset (vomiting and diarrhoea), low blood pressure (which may show as changes in concentration and reactions, light-headedness, sensation of pressure in the head, headache, drowsiness, dizziness when standing, weakness, changes to vision and dry mouth), hearing loss, ‘ringing’ in the ears, inflammation of the pancreas, kidney or blood vessels, itching, urticaria and rash. Furosemide may occasionally cause changes in the blood and your doctor may want to perform blood tests. If you are diabetic, Furosemide may interfere with your anti-diabetic medication.

Bone marrow depression and paraesthesia can occur rarely. Tetany can occur very rarely.

Serum cholesterol and triglyceride levels may rise during Furosemide treatment. During long term treatment, these will usually return to normal within six months.

Allergic reactions, including skin rashes, increased sensitivity to light, inflammation of the blood vessels, fever and shock occur rarely. If they occur, Furosemide therapy should be stopped.

Due to the fluid loss during the use of Furosemide, the electrolyte and water balance in the body might be disturbed. You might observe an increased thirst, headache, a fall in blood pressure, confusion, muscle cramps, muscle weakness and stomach upset.

Changes in blood volume and dehydration due to loss of fluid may occur, particularly in elderly patients.

Abnormal conditions in patients with obstructions to urinary flow might occur due to the extra fluid volumes excreted when using Furosemide.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. Storing Furosemide:
Do not store above 25°C. Once the bottle has been opened for more than 3 months it should not be used. Keep out of the reach and sight of children.

6. Further information:
Do not use after the expiry date printed on the label. Do not keep outdated medicine or medicine that is no longer wanted. Take it to your pharmacist for safe disposal. Always keep the medicine in the bottle in which it was given to you by your pharmacist.

This leaflet was last approved in June 2005.

3LF
Patient Information Leaflet
Furosemide 50 mg/5 ml Oral Solution

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:
1. What Furosemide is and what it is used for.
2. Before you take Furosemide.
3. How to take Furosemide.
4. Possible side effects.
5. Storing Furosemide.
6. Further information.

The active substance is Furosemide. The other ingredients are liquid maltitol, ethanol 96%, disodium hydrogen phosphate dodecahydrate, sodium hydroxide, citric acid monohydrate, flavour cherry (containing propylene glycol) and purified water.

Furosemide 50 mg/5 ml is available in 150 ml amber glass bottles.

Marketing Authorisation Holder and Manufacturer:
Pinewood Laboratories Limited trading as Pinewood Healthcare, Ballymacarby, Clonmel, Co. Tipperary, Ireland. PL 04917/0072-4

1. What Furosemide is and what it is used for:
Furosemide is an oral solution which contains 50 mg Furosemide in each 5 ml. Certain conditions which affect the heart, lungs, kidney, liver or blood vessels can lead to build up of water in the body. Furosemide belongs to a group of medicines called Diuretics which are used to reduce excess amounts of water in the body.

2. Before you take Furosemide:
Do not take Furosemide without first informing your doctor if you:
- ever had a bad reaction (hypersensitivity) to furosemide, sulphonamides or any of the ingredients listed.
- have liver problems particularly cirrhosis.
- have kidney problems.
- are pregnant or breast-feeding.
- have enlargement of the prostate gland.
- have low blood pressure, low blood salts or low blood volume.
- are diabetic.
- have gout.

Take special care with Furosemide if:
- urinary flow is partly obstructed. This could lead to fluid retention.
- you have low blood pressure (hypotension).
- you are at risk from a sharp fall in blood pressure.
- you have diabetes or are pre-disposed to diabetes.
- you are taking other medicines at the same time. See the section 'Taking other medicines' for more information.

The doctor may take blood samples in order to monitor how Furosemide is working while you are taking this medication.

Pregnancy and Breast-feeding:
Furosemide should be used with caution during pregnancy and whilst breast-feeding. Only to be used if strictly necessary.

Driving and using machines:
Mental alertness may be reduced and ability to drive or operate machinery may be impaired.

Important Information about some of the ingredients of Furosemide:
Ethanol
This medicinal product contains 10 vol % ethanol (alcohol), i.e., up to 442 mg of ethanol per 5 ml dose, equivalent to 8 ml of beer or 3 ml of wine per dose.
Harmful for 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.

Liquid Maltitol: If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3LF
Taking other medicines:
Inform your doctor if you are taking any of the following medicines:
Antibiotics, Lithium, ACE inhibitors (heart medication), medication for high and low blood pressure, non steroidal anti-inflammatory drugs (e.g. indomethacin, aspirin), muscle relaxants, salicylates, theophylline, glucocorticoids (prednisolone, dexamethasone), digoxin, cisplatin, sulfa drugs, phenylbut, carbasalazine, amnioglutethimide, carbonic anhydrase inhibitors, 2C sympathetic inhibitors (used to raise blood pressure), pantothenic acid, methotrexate, anti-diabetic medication and laxatives.

The dosage of some of your other medicines may need to be altered while using Furosemide as they may alter the effect of Furosemide. Your doctor will inform you of any changes required.

Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicines - even those received without a prescription.

3. How to take Furosemide:
For oral administration only (to be taken via the mouth). Use as directed by your doctor. Do not exceed the stated dose. It is best to take this medicine in the morning, or according to a schedule that will least affect your personal activities and sleep. Ask your doctor or pharmacist for advice on when best to take this medicine.

Adults:
The usual dose is 40 mg daily. This may need to be adjusted in order to determine the correct dose for you. Take exactly what is prescribed for you by your doctor.

Children:
Children’s doses may be lower (1 to 3 mg/kg body weight) but they must not take more than 40 mg a day.

Elderly:
Dosage is generally titrated until the required response is achieved as furosemide is generally eliminated more slowly from the body.

Continue taking this medicine until your doctor tells you to stop.

If you take more Furosemide than you should:
You should contact a doctor or hospital immediately.

If you forget to take Furosemide:
Take the next dose as soon as you remember than continue taking as normal the following morning.

4. Possible side effects:
Along with the desired effects, a medicine can also have some unwanted effects. Side effects are generally minor and Furosemide is well tolerated. Although not all these side effects may occur, if they do then you may need medical attention. Nausea, tiredness, stomach upset (vomiting and diarrhoea), low blood pressure (which may show as changes in concentration and reaction, light-headedness, sensation of pressure in the head, headache, drowsiness, dizziness, dizziness when standing, weakness, changes in vision and dry mouth), hearing loss, 'ringing' in the ears, inflammation of the pancreas, kidney or blood vessels, itching, urticaria and hives. Furosemide may occasionally cause changes in the blood and your doctor may want to perform blood tests. If you are diabetic, Furosemide may interfere with your anti-diabetic medication.

Bone marrow depression and paraesthesiae can occur rarely. Tetany can occur very rarely.

Serum cholesterol and triglyceride levels may rise during Furosemide treatment. During long term treatment, these will usually return to normal within six months.

Allergic reactions, including skin rashes, increased sensitivity to light, inflammation of the blood vessels, fever and shock occur rarely. If they occur, Furosemide therapy should be stopped.

Due to the fluid loss during the use of Furosemide, the electrolyte and water balance in the body might be disturbed. You might observe an increased thirst, headache, a fall in blood pressure, confusion, muscle cramps, muscle weakness and stomach upset.

Changes in blood volume and dehydration due to loss of fluid may occur, particularly in elderly patients.

Aggravation of conditions in patients with obstructions to urinary flow may occur due to the extra fluid volumes excreted when using Furosemide.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. Storing Furosemide:
Do not store above 25°C. Once the bottle has been opened for more than 3 months it should not be used. Keep out of the reach and sight of children.

6. Further information:
Do not use after the expiry date printed on the label. Do not keep outdated medicine or medicine that is no longer wanted. Take it to your pharmacist for safe disposal. Always keep the medicine in the bottle in which it was given to you by your pharmacist.

This leaflet was last approved in June 2005.
Furosemide
20 mg/5 ml
Oral Solution

150 ml

Please read enclosed leaflet carefully for further information.

Each 5 ml of oral solution contains 20 mg of the active ingredient Furosemide. The product also contains: ethanol 96% and liquid maltitol. See leaflet for further information.

For Oral Administration. Take exactly as directed by your doctor. Do not exceed the stated dose.

Do not store above 25°C. Once the bottle has been opened for more than 3 months, the product should not be used. Do not keep outdated medicines, or medicine that is no longer wanted. Take it to your pharmacist for safe disposal.

Keep all medicines out of reach and sight of children.

Marketing Authorisation Holder:
Pinewood Laboratories Ltd., Ballymacarbry, Clonmel, Co.Tipperary, Ireland.
PL04917/0072 3LL
Furosemide
40 mg/5 ml
Oral Solution
150 ml

Please read enclosed leaflet carefully for further information.

Each 5 ml of oral solution contains 40 mg of the active ingredient Furosemide. The product also contains: ethanol 96% and liquid maltitol. See leaflet for further information.

For Oral Administration. Take exactly as directed by your doctor.
Do not exceed the stated dose.

Do not store above 25°C.
Once the bottle has been opened for more than 3 months, the product should not be used. Do not keep outdated medicine, or medicine that is no longer wanted. Take it to your pharmacist for safe disposal.

Keep all medicines out of reach and sight of children.

Marketing Authorisation Holder:
Pinewood Laboratories Ltd., Ballymacarbry, Clonmel, Co.Tipperary, Ireland.
PL 04917/0073 3LL

POM
Please read enclosed leaflet carefully for further information.

Each 5 ml of oral solution contains 50 mg of the active ingredient Furosemide. The product also contains: ethanol 96% and liquid maltitol. See leaflet for further information.

For Oral Administration. Take exactly as directed by your doctor. Do not exceed the stated dose.

Do not store above 25°C. Once the bottle has been opened for more than 3 months, the product should not be used. Do not keep outdated medicine, or medicine that is no longer wanted. Take it to your pharmacist for safe disposal.

Keep all medicines out of reach and sight of children.

PL 04917/0074 3LL

Product Licence holder: Pinewood Healthcare

POM