

**SALBUTAMOL 1MG/ML NEBULISER SOLUTION
SALBUTAMOL 2MG/ML NEBULISER SOLUTION**

PL 08137/0083 & 0131

UKPAR

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SALBUTAMOL 1MG/ML NEBULISER SOLUTION SALBUTAMOL 2MG/ML NEBULISER SOLUTION

PL 08137/0083 & 0131

LAY SUMMARY

The MHRA granted Neolab Limited Marketing Authorisations (licences) for the medicinal products Salbutamol 1mg/ml Nebuliser Solution (PL 08137/0083) and Salbutamol 2mg/ml Nebuliser Solution (PL 08137/0131) on the 13th of July 2006. These prescription only medicines (POM) are used to provide short-acting (4-6 hour) bronchodilatation with a fast onset (within 5 minutes) in reversible airways obstruction; and for use in the routine management of chronic bronchospasm unresponsive to conventional therapy, and in the treatment of acute severe asthma.

Salbutamol 1mg/ml and 2mg/ml Nebuliser Solution contains the active ingredient salbutamol (as sulphate) which is selective β_2 -agonist which helps with breathing and the respiratory function of the lungs.

The data presented to the MHRA, pre licensing, demonstrated that Salbutamol 1mg/ml and 2mg/ml Nebuliser Solution are equivalent to the approved products, Ventolin Nebules 2.5mg (equivalent to 1mg/ml) and 5mg (equivalent to 2mg/ml). Salbutamol 1mg/ml and 2mg/ml Nebuliser Solution can therefore be used interchangeably with Ventolin Nebules 2.5mg and 5mg (PL 10949/0085-6).

No new or unexpected safety concerns arose from these applications. It was, therefore, judged that the benefits of taking Salbutamol 1mg/ml and 2mg/ml Nebuliser Solution outweigh the risks. Hence, Marketing Authorisations have been granted.

**SALBUTAMOL 1MG/ML NEBULISER SOLUTION
SALBUTAMOL 2MG/ML NEBULISER SOLUTION**

PL 08137/0083 & 0131

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 Salbutamol 1mg/ml and 2mg/ml Nebuliser Solution, (PL 08137/0083 & 0131) to Neolab Limited on 13th of July 2006. The products are prescription only medicines.

The applications were submitted as abridged applications according to article 10.1 [formerly article 10.1(a)(iii)] of Directive 2001/83/EC, claiming essential similarity to the original products Ventolin Nebules 2.5mg and 5mg (PL 10949/0085-6).

The products contain the active ingredient salbutamol (as sulphate) and are used to provide short-acting (4-6 hour) bronchodilatation with a fast onset (within 5 minutes) in reversible airways obstruction; and for use in the routine management of chronic bronchospasm unresponsive to conventional therapy, and in the treatment of acute severe asthma.

Salbutamol is a short acting β_2 adrenergic bronchodilator that has been used for over 20 years for the control of asthma symptoms. Salbutamol preparations are currently available in a range of dosage forms (oral tablets and liquids, as metered dose inhalers and for parenteral use) including nebulising solutions.

PHARMACEUTICAL ASSESSMENT

PL NUMBER: 08137/0083 & 08137/0131
PRODUCT: Salbutamol 1mg/ml Nebuliser Solution (0083)
Salbutamol 2mg/ml Nebuliser Solution (0131)
ACTIVE: Salbutamol sulphate
COMPANY: Neolab Limited
LEGAL STATUS: POM

1. INTRODUCTION

These are abridged applications for Marketing Authorisations in the UK submitted under Article 10.1(a)(iii) of Directive 2001/83 (as amended), first paragraph so called generic application.

The original products are listed as Ventolin Nebules 2.5mg and 5mg respectively. The licence holder for both products is Glaxo Wellcome. The Ventolin Nebules 2.5mg licence PL 10949/0085 was granted on 1st March 1994, and was previously marketed by Allen & Hanbury under licence PL 00045/0123 granted on the 10th June 1981. The Ventolin Nebules 5mg licence PL 10949/0086 was granted on 1st March 1994, and was previously marketed by Allen & Hanbury under licence PL 00045/0133 granted 15th May 1987.

No bioequivalence studies have been performed on these products.

2. ACTIVE SUBSTANCE

2.1 Specification

The active substance manufacturer is stated. The active substance has a Drug Master File (DMF) and a letter of access has been provided for use with PL 08137/0083 and 08137/0131. Salbutamol sulphate has a European Pharmacopoeia monograph.

The finished product manufacturer tests all batches to the European Pharmacopoeia monograph. Relevant certificates of analysis have been supplied from the finished product manufacturer demonstrating compliance.

2.2 Analytical test methods

The test methods used are those described in the pharmacopoeia and an in-house method for the determination of residual solvents.

2.3 Analytical test method validation

Validation has been performed for the analytical methods that are described in the pharmacopoeia. The residual solvent method validation is that included in the DMF.

3. DRUG PRODUCT

3.1 Composition

The composition of the two proposed strengths are summarised in table 1. The finished products are clear colourless to light yellow solutions. The solutions are packed into plastic (polyethylene) form-fill-seal ampoules, a strip of which is over-wrapped in a triple laminated pouch.

Table 1

Formulation	Function	Reference
Salbutamol (as sulphate)	Active	Ph. Eur.
Sodium chloride	Isotonicity agent	Ph. Eur.
Sulphuric acid (1N)	pH adjustment	Ph. Eur.
Water for injection	Solvent	Ph. Eur.

3.2 Pharmaceutical Development

3.2.1 Components

The salbutamol nebuliser solutions are products containing excipients which are commonly used and are the same as those present in the original product, referenced from the SPC. The function of each of the excipients has been listed.

3.2.2 Formulation development

The formulation for the salbutamol nebuliser solutions is entirely based on the original product. Salbutamol sulphate is freely soluble in water. To maintain stability the pH of the solution was adjusted. This was within the reported stability limits of salbutamol sulphate in solution.

The products are very simple solution formulations.

Batches prepared using commercial equipment were compared to the original product for both strengths on description, pH, colour index, related substances, osmolality, aerodynamic assessment and assay. The salbutamol nebuliser solutions were very similar to the original products.

The data provided is adequate as far as basic development goes but is not sufficient to demonstrate pharmaceutical equivalence.

3.2.3 Manufacturing process development

Manufacturing process development is a simple description of the manufacturing process.

This is considered to be satisfactory for a product of this type.

3.2.4 Compatibility

The salbutamol nebuliser solutions are single dose products which can be diluted before use in a continuously operating nebuliser.

The salbutamol nebuliser solutions were shown to be compatible with normal saline when stored for at room temperature, determined on assay, related substances, colour index and aerodynamic assessment. This was demonstrated on three batches of the 2.5mg/2.5ml and 5.0mg/2.5ml, in comparison to the reference products.

3.3 Manufacture

3.3.1 Manufacturer(s)

A suitable manufacturing licence has been included. A positive inspection letter has been supplied from the MHRA dated 2004 covering the products in this application.

It appears that this site has not been used to manufacture form-fill-seal products for any previously approved UK licences.

3.3.2 Batch formula

The batch formula has been presented for the two strengths. The maximum batch size is stated.

There are no overages in the formula.

3.3.3 Manufacturing process and process controls

A flow diagram detailing the manufacturing process has been provided. A written summary of the process is also included.

3.3.4 In-process controls

The majority of the in-process checks are satisfactory.

3.3.5 Control of critical steps and intermediates

Due to the simplicity of the formulation the microbiological quality is the only step deemed to be critical. The requirements are the European Pharmacopoeia category 2.

Various controls are operated to ensure compliance these are satisfactory.

During the validation work all batches were shown to be sterile. The original product is also sterile as detailed in the SPC.

3.3.6 Process validation or evaluation

Process validation has been completed on three batches for both strengths.

Validation of the filling process has been shown by assessment of fill volume, assay, pH, colour and sterility, with the results being consistent and within the set limits.

Adequate validation data has been presented for the sterilisation process used on the equipment.

3.4 Control of materials

3.4.1 Control of excipients

Sodium chloride, sulphuric acid and water for injections have monographs in the European Pharmacopoeia. Certificates of analysis have been provided from the finished product manufacturer and excipient manufacturers. The finished product manufacturer has confirmed that all batches will be tested to confirm compliance to the European Pharmacopoeia monographs.

Relevant details have been provided on the tests performed and the sampling procedures.

3.5 Control of drug product

3.5.1 Specification

The finished product specifications for the nebulisers are provided for release and shelf-life.

The specification covers the requirements of the BP monograph for salbutamol nebuliser solution.

3.5.2 Analytical procedures

All the details have been provided for the pharmacopoeia and non-pharmacopoeia methods. The methods for assay and related substances are more suitable than the methods described in the pharmacopoeia.

3.5.3 Validation

The assay for salbutamol sulphate has been validated. The method has been shown to be accurate and precise. Robustness has been demonstrated in reference to composition of buffer, pH, flow rate and column temperature. The test solutions were shown to be stable for up to 24 hours.

The assay for related substances has been validated for the stated known impurities. The method has been shown to be accurate and precise. The detection limits and the quantitation limits have been determined.

Specificity has been shown in relation to the salbutamol sulphate known impurities. Robustness has been shown for pH, flow rate and temperature.

The sterility test has been validated in-line with the requirements of the European Pharmacopoeia.

3.5.4 Batch analyses

Batch analyses data have been provided for three batches of both strengths. These are the batches produced for the validation.

3.6 Container closure system

The plastic form-fill seal ampoule is an aseptically blown, filled and sealed ampoule made from polyethylene granules (polyethylene synthetic resin). The strips of ampoules are over-wrapped in a triple laminated pouch of which the three laminate layers are composed of polyester, aluminium and polyethylene.

Specifications and certificates of analysis have been provided for the polyethylene and the laminate pouches. The tests listed are those performed by the finished product manufacturer upon receipt of new batches of packaging materials. The product complies with the specification for polyethylene without additives.

Confirmation has been supplied on compliance to the directives on contact materials from the supplier. Details of the test methods have also been supplied.

3.7 Stability

Stability data has been provided for the three validation batches of both strengths packed in the proposed packaging. The storage conditions were 25°C/60%RH and 40°C/75%RH.

Long term testing is planned up to 24 months and accelerated testing has been completed up to 6 months.

The parameters tested remain in specification for all batches with the exception of individual unknown impurities. At 25°C/60%RH one batch is out of specification at 12 months with another batch at 24 months and at 40°C/75%RH two batches are out of specification after 3 months.

The proposed shelf-life of 2 years unopened and 3 months after opening the foil over-wrap is acceptable on the basis of the data provided.

3.8 Other information

3.8.1 Biostudies

No biostudies have been performed on these products.

For further information see medical assessment report.

3.8.2 Essential similarity

The Salbutamol Nebuliser Solutions are essentially similar in terms of the qualitative and quantitative composition to Ventolin Nebules.

4. PRODUCT LITERATURE

4.1 SPC

The SPC is satisfactory.

4.2 PIL

The PIL is satisfactory.

4.3 LABEL

The labels are satisfactory.

5. ADMINISTRATIVE

5.1 MAA form

The MAA form is satisfactory.

5.2 Quality overall summary

Has been completed by a suitable expert. The report is a summary of the module, with a few critical comments.

6. CONCLUSIONS AND ADVICE

A marketing authorisation can be granted.

Pharmaceutical Assessor

Original assessment: 8th November 2004

Response assessment: 1st August 2005

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

LICENCE NO:	PL 08137/0083-0131
PROPRIETARY NAME:	Salbutamol 1mg/ml Nebuliser Solution (0083) Salbutamol 2 mg/ml Nebuliser Solution (0131)
ACTIVE(S):	Salbutamol sulphate
COMPANY NAME:	Neolab Ltd
E.C. ARTICLE:	10.1
LEGAL STATUS:	POM

1. INTRODUCTION

These are national abridged standard applications for a marketing authorisation for Salbutamol 1 mg/ml nebuliser solution (PL 08137/0083) and Salbutamol 2 mg/ml nebuliser solution (PL 08137/0131). The applicant claims essential similarity to Ventolin nebuliser 2.5 mg (PL 10949/0085) and 5 mg (PL 10949/0086), licensed originally to Allen & Highbury in 1987 (PL 00045/0133) and 1981 (PL 0045/0123). Both licenses were taken over by Glaxo Wellcome UK Ltd in 1994. The applications are made under article 10.1(a)(iii), first paragraph, of EC Directive 83/2001. A subsequent mutual recognition procedure has not been considered.

2. BACKGROUND

Salbutamol is a short acting β_2 adrenergic bronchodilator that has been used for over 20 years for the control of asthma symptoms. Salbutamol preparations are currently available in a range of dosage forms (oral tablets and liquids, as metered dose inhalers and for parenteral use) including nebulising solutions.

3. INDICATIONS

Salbutamol is a selective β_2 -agonist providing short-acting (4-6 hour) bronchodilatation with a fast onset (within 5 minutes) in reversible airways obstruction.

Salbutamol Nebuliser Solutions are indicated for use in the routine management of chronic bronchospasm unresponsive to conventional therapy, and in the treatment of acute severe asthma.

4. DOSE & DOSE SCHEDULE

For inhalation use.

To be used with a suitable nebuliser device under the direction of a physician.

Adults (and the elderly): 2.5mg to 5mg salbutamol up to four times a day. Up to 40mg per day can be given under strict medical direction in hospital.

Children: 2.5mg to 5mg up to four times a day.

Infants under 18 months old: The clinical efficacy of nebulised salbutamol is uncertain. As transient hypoxia may occur supplemental oxygen therapy should be considered.

Salbutamol Nebulisers Solutions are intended to be used undiluted. However, if prolonged delivery time (more than 10 minutes) is required, the solution may be diluted with sterile normal saline.

5. TOXICOLOGY

No new preclinical data have been submitted for these applications and none are required.

6. CLINICAL PHARMACOLOGY

6.1 PHARMACOKINETICS

When salbutamol is taken by the inhalation route only about 10% - 20% of the dose is deposited in the airways, with the remainder either being retained in the delivery system or swallowed.

Inhaled Salbutamol has a fast onset of action (within 5 – 10 minutes of inhalation) and lasts 4-6 hours in most patients.

Salbutamol does not appear to be metabolised in the lung. The swallowed part of the salbutamol dose is absorbed from the gastrointestinal tract and is subject to first-pass metabolism in the liver; about half is excreted in the urine as an inactive sulphate conjugate.

6.2 PHARMACODYNAMICS

Salbutamol is a selective beta-2-adrenoceptor agonist with effects on bronchial muscle.

6.3 BIOEQUIVALENCE

No bioavailability or bioequivalence studies have been conducted or are required as these products are aqueous solution of salbutamol for use in a nebuliser. The salbutamol nebuliser solutions are essentially similar in terms of quantitative and qualitative composition to the reference products.

7. EFFICACY

No new efficacy data have been submitted and none are required for these applications.

8. SAFETY

No new safety data have been submitted and none are required for these applications.

9. EXPERT REPORT

A clinical overview by an appropriate expert has been submitted. The report is considered satisfactory.

10. SUMMARY OF PRODUCT CHARACTERISTICS

The SPC is acceptable.

11. PATIENT INFORMATION LEAFLET

The PIL is acceptable.

12. LABELLING

The Labels are acceptable.

13. MARKETING APPLICATION FORM

This is satisfactory.

14. DISCUSSION

These are abridged applications for the marketing authorisation for Salbutamol 1 mg/ml nebuliser solution and Salbutamol 2 mg/ml nebuliser solution claiming essential similarity to Ventolin nebules 2.5 mg and 5 mg respectively which have been licensed in the UK for more than 10 years.

Salbutamol is a short acting β_2 adrenergic bronchodilator that has been used for over 20 years for the control of asthma symptoms.

No bioequivalence studies have been conducted or are required as these products are aqueous solution of salbutamol for use in a nebuliser. The salbutamol nebuliser solutions are essentially similar in terms of quantitative and qualitative composition to the reference products. No new efficacy or safety data have been submitted for this application.

Only minor changes to the product literature were required.

15. CONCLUSIONS

The efficacy and safety of Salbutamol 1 mg/ml & 2 mg/ml nebuliser solution are satisfactory for the grant of product licence.

Medical Assessor
29th March 2005

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Salbutamol 1 mg/ml & 2 mg/ml nebuliser solution are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

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

EFFICACY

No bioavailability or bioequivalence studies have been conducted or are required as these products are aqueous solution of salbutamol for use in a nebuliser. The salbutamol nebuliser solutions are essentially similar in terms of quantitative and qualitative composition to the reference products Ventolin Nebules.

No new efficacy or safety data have been submitted for this application. No new or unexpected safety concerns arise from these applications.

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

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The risk benefit is therefore considered to be positive.

**SALBUTAMOL 1MG/ML NEBULISER SOLUTION
SALBUTAMOL 2MG/ML NEBULISER SOLUTION**

PL 08137/0083 & 0131

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 11/05/2004
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 25/05/2004
3	Following assessment of the application the MHRA requested further information relating to the dossier on 28/02/2005, 31/03/2005, 23/09/2005, 08/12/2005
4	The applicant responded to the MHRA's requests, providing further information relating to the dossier on 25/05/2005, 28/11/2005, 22/05/2006
5	The application was determined on 13/07/2006

**SALBUTAMOL 1MG/ML NEBULISER SOLUTION
SALBUTAMOL 2MG/ML NEBULISER SOLUTION**

PL 08137/0083 & 0131

STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

**SALBUTAMOL 1MG/ML NEBULISER SOLUTION
SALBUTAMOL 2MG/ML NEBULISER SOLUTION**

PL 08137/0083 & 0131

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Salbutamol 1mg/ml Nebuliser Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each nebule contains 2.5mg / 2.5ml salbutamol (as sulphate).

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser Solution (for use via a nebuliser).

Plastic ampoule containing 2.5 ml of a clear sterile solution containing 2.5mg salbutamol (as sulphate) in normal saline

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Salbutamol is a selective β_2 -agonist providing short-acting (4-6 hour) bronchodilatation with a fast onset (within 5 minutes) in reversible airways obstruction.

Salbutamol Nebuliser Solutions are indicated for use in the routine management of chronic bronchospasm unresponsive to conventional therapy, and in the treatment of acute severe asthma.

4.2 Posology and method of administration

For inhalation use.

To be used with a suitable nebuliser device under the direction of a physician.

Adults (and the elderly): 2.5mg to 5mg salbutamol up to four times a day. Up to 40mg per day can be given under strict medical direction in hospital.

Children: 2.5mg to 5mg up to four times a day.

Infants under 18 months old: The clinical efficacy of nebulised salbutamol is uncertain. As transient hypoxia may occur supplemental oxygen therapy should be considered.

Salbutamol Nebulisers Solutions are intended to be used undiluted. However, if prolonged delivery time (more than 10 minutes) is required, the solution may be diluted with sterile normal saline.

4.3 Contraindications

Hypersensitivity to salbutamol or to any of the excipients.

Salbutamol Nebuliser Solutions are contraindicated for use in the management of premature labour and threatened abortion.

4.4 Special warnings and precautions for use

Potentially serious hypokalaemia has been reported in patients taking beta-2-agonist therapy. Particular caution is advised in patients with severe asthma as hypokalaemia may be potentiated in hypoxic patients and those treated with xanthine derivatives, steroids, diuretics and long-term laxatives. In these groups of patients serum potassium levels should be monitored.

In severe or unstable asthma bronchodilators should not be the only or main treatment. Severe asthma requires specialist medical assessment.

Patients should be advised to seek medical advice if their treatment ceases to be effective, more inhalations than usual are required and/or their asthma seems to be getting worse. Patients should not increase their dose without medical advice.

Salbutamol should be administered cautiously to patients with thyrotoxicosis.

Salbutamol Nebuliser Solutions should be used with care in patients known to have received large doses of other sympathomimetic drugs.

In common with other β -adrenoceptor agonists, salbutamol can induce reversible metabolic changes such as increased blood glucose levels. Diabetic patients may be unable to compensate for the increase in blood glucose and the development of ketoacidosis has been reported. Concurrent administration of corticosteroids can exaggerate this effect.

A small number of cases of acute angle-closure glaucoma have been reported in patients treated with a combination of nebulised salbutamol and ipratropium bromide. A combination of nebulised salbutamol with nebulised anticholinergics should therefore be used cautiously. Patients should receive adequate instruction in correct administration and be warned not to let the solution or mist, enter their eyes.

Patients receiving treatment at home should seek medical advice if treatment with nebulised salbutamol becomes less effective. The dosage or frequency of administration should only be increased on medical advice.

4.5 Interaction with other medicinal products and other forms of interaction

Salbutamol and beta-blockers (i.e propranolol) should not usually be prescribed together.

Hypokalaemia occurring with beta-2-agonist therapy may be exacerbated by treatment with xanthines, steroids, diuretics and long-term laxatives.

4.6 Pregnancy and lactation

Salbutamol should not be used in pregnancy and lactation unless the expected benefit to the mother is thought to outweigh the risk to the foetus.

The safe use of inhaled Salbutamol during pregnancy has not been established but it is reported that in animal studies at high doses there is evidence of harmful effects to the foetus.

Careful consideration should be given to the use of Salbutamol in nursing mothers, as it is not known whether salbutamol is distributed into breast milk.

4.7 Effects on ability to drive and use machines

None reported.

4.8 Undesirable effects

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with an alternative presentation or a different fast-acting inhaled bronchodilator. The preparation should be discontinued immediately, the patient assessed and, if necessary, alternative therapy instituted.

Solutions which are not of neutral pH may rarely cause bronchospasm.

Hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension and collapse have been reported very rarely.

Potentially serious hypokalaemia may result from β_2 -agonist therapy.

Salbutamol Nebuliser Solutions may cause a fine tremor of skeletal muscle, usually the hands are most obviously affected. This effect is dose-related and is common to all β -adrenergic stimulants.

Tachycardia, with or without peripheral vasodilatation, may rarely occur. In common with other β_2 agonists, cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles) have been reported in association with the use of salbutamol, usually in susceptible patients.

Headaches have occasionally been reported.

Mouth and throat irritation may occur with inhaled salbutamol.

As with other β_2 -agonists hyperactivity in children has been reported rarely.

There have been very rare reports of muscle cramps.

4.9 Overdose

The preferred antidote to overdosage with salbutamol is a cardioselective β -blocking agent, but β -blocking drugs should be used with caution in patients with a history of bronchospasm.

Hypokalaemia may occur following overdose with salbutamol. Serum potassium levels should be monitored.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

R03A C02

Salbutamol is a selective beta-2-adrenoceptor agonist with effects on bronchial muscle.

5.2 Pharmacokinetic properties

When salbutamol is taken by the inhalation route only about 10% - 20% of the dose is deposited in the airways, with the remainder either being retained in the delivery system or swallowed.

Inhaled Salbutamol has a fast onset of action (within 5 – 10 minutes of inhalation) and lasts 4-6 hours in most patients.

Salbutamol does not appear to be metabolised in the lung. The swallowed part of the salbutamol dose is absorbed from the gastrointestinal tract and is subject to first-pass metabolism in the liver; about half is excreted in the urine as an inactive sulphate conjugate.

5.3 Preclinical safety data

No additional information.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sulphuric acid to adjust pH
Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years unopened.
3 months after opening the foil over-wrap.

6.4 Special precautions for storage

Store in the original package.
The ampoules should be protected from light after removal from the foil over-wrap.

6.5 Nature and contents of container

Plastic polyethylene ampoules in strips of 5 ampoules, with a protective foil over-wrap.
Available in boxes containing 20 ampoules.

6.6 Special precautions for disposal

Nebulisers should be used in a well ventilated room as it is usual for some nebulised drug to be released into the local environment.

Dilution: May be diluted with sterile sodium chloride solution, (normal saline) if required.

For instructions on the use of this product refer to the Patient Information Leaflet.

7 MARKETING AUTHORISATION HOLDER

Neolab Limited
57 High Street
Odiham,
Hampshire
RG29 1LF
England

8 MARKETING AUTHORISATION NUMBER(S)

PL 08137/0083

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/07/2006

10 DATE OF REVISION OF THE TEXT

13/07/2006

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Salbutamol 2mg/ml Nebuliser Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each nebule contains 5mg / 2.5ml salbutamol (as sulphate).

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser Solution (for use via a nebuliser).

Plastic ampoule containing 2.5 ml of a clear sterile solution containing 5mg salbutamol (as sulphate) in normal saline.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Salbutamol is a selective β_2 -agonist providing short-acting (4-6 hour) bronchodilatation with a fast onset (within 5 minutes) in reversible airways obstruction.

Salbutamol Nebuliser Solutions are indicated for use in the routine management of chronic bronchospasm unresponsive to conventional therapy, and in the treatment of acute severe asthma.

4.2 Posology and method of administration

For inhalation use.

To be used with a suitable nebuliser device under the direction of a physician.

Adults (and the elderly): 2.5mg to 5mg salbutamol up to four times a day. Up to 40mg per day can be given under strict medical direction in hospital.

Children: 2.5mg to 5mg up to four times a day.

Infants under 18 months old: The clinical efficacy of nebulised salbutamol is uncertain. As transient hypoxia may occur supplemental oxygen therapy should be considered.

Salbutamol Nebulisers Solutions are intended to be used undiluted. However, if prolonged delivery time (more than 10 minutes) is required, the solution may be diluted with sterile normal saline.

4.3 Contraindications

Hypersensitivity to salbutamol or to any of the excipients.

Salbutamol Nebuliser Solutions are contraindicated for use in the management of premature labour and threatened abortion.

4.4 Special warnings and precautions for use

Potentially serious hypokalaemia has been reported in patients taking beta-2-agonist therapy. Particular caution is advised in patients with severe asthma as hypokalaemia may be potentiated in hypoxic patients and those treated with xanthine derivatives, steroids, diuretics and long-term laxatives. In these groups of patients serum potassium levels should be monitored.

In severe or unstable asthma bronchodilators should not be the only or main treatment. Severe asthma requires specialist medical assessment.

Patients should be advised to seek medical advice if their treatment ceases to be effective, more inhalations than usual are required and/or their asthma seems to be getting worse. Patients should not increase their dose without medical advice.

Salbutamol should be administered cautiously to patients with thyrotoxicosis.

Salbutamol Nebuliser Solutions should be used with care in patients known to have received large doses of other sympathomimetic drugs.

In common with other β -adrenoceptor agonists, salbutamol can induce reversible metabolic changes such as increased blood glucose levels. Diabetic patients may be unable to compensate for the increase in blood glucose and the development of ketoacidosis has been reported. Concurrent administration of corticosteroids can exaggerate this effect.

A small number of cases of acute angle-closure glaucoma have been reported in patients treated with a combination of nebulised salbutamol and ipratropium bromide. A combination of nebulised salbutamol with nebulised anticholinergics should therefore be used cautiously. Patients should receive adequate instruction in correct administration and be warned not to let the solution or mist, enter their eyes.

Patients receiving treatment at home should seek medical advice if treatment with nebulised salbutamol becomes less effective. The dosage or frequency of administration should only be increased on medical advice.

4.5 Interaction with other medicinal products and other forms of interaction

Salbutamol and beta-blockers (i.e propranolol) should not usually be prescribed together.

Hypokalaemia occurring with beta-2-agonist therapy may be exacerbated by treatment with xanthines, steroids, diuretics and long-term laxatives.

4.6 Pregnancy and lactation

Salbutamol should not be used in pregnancy and lactation unless the expected benefit to the mother is thought to outweigh the risk to the foetus.

The safe use of inhaled Salbutamol during pregnancy has not been established but it is reported that in animal studies at high doses there is evidence of harmful effects to the foetus.

Careful consideration should be given to the use of Salbutamol in nursing mothers, as it is not known whether salbutamol is distributed into breast milk.

4.7 Effects on ability to drive and use machines

None reported.

4.8 Undesirable effects

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with an alternative presentation or a different fast-acting inhaled bronchodilator. The preparation should be discontinued immediately, the patient assessed and, if necessary, alternative therapy instituted.

Solutions which are not of neutral pH may rarely cause bronchospasm.

Hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension and collapse have been reported very rarely.

Potentially serious hypokalaemia may result from β_2 -agonist therapy.

Salbutamol Nebuliser Solutions may cause a fine tremor of skeletal muscle, usually the hands are most obviously affected. This effect is dose-related and is common to all β -adrenergic stimulants.

Tachycardia, with or without peripheral vasodilatation, may rarely occur. In common with other β_2 agonists, cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles) have been reported in association with the use of salbutamol, usually in susceptible patients.

Headaches have occasionally been reported.

Mouth and throat irritation may occur with inhaled salbutamol.

As with other β_2 -agonists hyperactivity in children has been reported rarely.

There have been very rare reports of muscle cramps.

4.9 Overdose

The preferred antidote to overdose with salbutamol is a cardioselective β -blocking agent, but β -blocking drugs should be used with caution in patients with a history of bronchospasm.

Hypokalaemia may occur following overdose with salbutamol. Serum potassium levels should be monitored.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

R03A C02

Salbutamol is a selective beta-2-adrenoceptor agonist with effects on bronchial muscle.

5.2 Pharmacokinetic properties

When salbutamol is taken by the inhalation route only about 10% - 20% of the dose is deposited in the airways, with the remainder either being retained in the delivery system or swallowed.

Inhaled Salbutamol has a fast onset of action (within 5 – 10 minutes of inhalation) and lasts 4-6 hours in most patients.

Salbutamol does not appear to be metabolised in the lung. The swallowed part of the salbutamol dose is absorbed from the gastrointestinal tract and is subject to first-pass metabolism in the liver; about half is excreted in the urine as an inactive sulphate conjugate.

5.3 Preclinical safety data

No additional information.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sulphuric acid to adjust pH
Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years unopened.
3 months after opening the foil over-wrap.

6.4 Special precautions for storage

Store in the original package.
The ampoules should be protected from light after removal from the foil over-wrap.

6.5 Nature and contents of container

Plastic polyethylene ampoules in strips of 5 ampoules, with a protective foil over-wrap.
Available in boxes containing 20 ampoules

6.6 Special precautions for disposal

Nebulisers should be used in a well ventilated room as it is usual for some nebulised drug to be released into the local environment.

Dilution: May be diluted with sterile sodium chloride solution, (normal saline) if required.

For instructions on the use of this product refer to the Patient Information Leaflet.

7 MARKETING AUTHORISATION HOLDER

Neolab Limited
57 High Street
Odiham,
Hampshire
RG29 1LF
England

8 MARKETING AUTHORISATION NUMBER(S)

PL 08137/0131

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/07/2006

10 DATE OF REVISION OF THE TEXT

13/07/2006

SALBUTAMOL 1MG/ML NEBULISER SOLUTION SALBUTAMOL 2MG/ML NEBULISER SOLUTION

PL 08137/0083 & 0131

PRODUCT INFORMATION LEAFLET

Read all of this leaflet carefully before you start taking this medicine.

SALBUTAMOL 1mg/ml and 2mg/ml NEBULISER SOLUTIONS

PATIENT INFORMATION LEAFLET

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your 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:

- What salbutamol is and what it is used for.
- Before you use your Salbutamol Nebuliser Solution.
- How to use your Salbutamol Nebuliser Solution.
- Possible side effects.
- Storing your Salbutamol Nebuliser Solution.
- Further information

The name of the medicine is **Salbutamol Nebuliser Solution** (also referred to as Salbutamol solution or salbutamol throughout this leaflet).

- The active substance is salbutamol (as sulphate).
- The other ingredients are sodium chloride, sulphuric acid as pH adjuster, and water.

Marketing Authorisation Holder and manufacturer responsible for EU release: Neolab Ltd, 57 High Street, Odham, Hants RG29 1LF.

1. What Salbutamol is and what it is used for

Salbutamol Nebuliser Solution is a liquid which when used in a Nebulising device is converted into a mist which can then be inhaled. There are two strengths available, 2.5mg of the active ingredient salbutamol in 2.5ml of solution and 5mg of salbutamol in 2.5ml of solution.

Each pack contains 20 ampoules, each containing 2.5ml of solution.

Salbutamol belongs to a group of medicines known as beta adrenoceptor agonists (or bronchodilators) which are used to make breathing easier by opening up the airways in the lungs.

Salbutamol is used for the management of the symptoms of severe asthma and for other chest illnesses. It is usually used in asthma when other forms of treatment are no longer enough.

Salbutamol Nebuliser Solution is also given to treat severe attacks of asthma.

2. Before you use your Salbutamol Nebuliser Solution

Do not use Salbutamol if any of the following apply to you:

- If you are hypersensitive (allergic) to salbutamol or any of the other ingredients in this solution (see above).
- If you are pregnant or trying to get pregnant or breast feeding a baby.

Take special care when using Salbutamol:

- If you have a thyroid condition,
- If you are diabetic.

If you have any of these conditions make sure you tell your doctor before using this product.

Pregnancy and breast-feeding:
Please inform your doctor or pharmacist for advice before taking any medicine.

Taking other medicines
Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicines, even those not prescribed but bought without a prescription.

Care is needed if:

- you are taking beta-blockers. These are not usually given when salbutamol is being taken.
- you are taking xanthines, steroids, diuretics (water tablets) or long term laxatives.

3. How to use your Salbutamol Nebuliser Solution

This product is for inhalation use.

Always follow your doctor's advice on how and when to use your nebuliser and how many you should use. Do not use more than your doctor has told you to. Ensure that you know how to use your Nebuliser properly. More detailed instructions on the use of these ampoules are given below.

Read and follow the instructions on the pharmacist's label. If you are not sure about anything please ask your doctor or pharmacist.

Adults, Elderly and Children: The usual dose is 2.5mg to 5mg salbutamol used up to 4 times a day.

For severe attacks in hospital a higher dose may be given.

Do not take more doses than your doctor has prescribed or use your nebuliser more often than you are told. It is very important that you inhale each dose exactly as instructed.

If your usual dose is not working as well as before or your asthma symptoms get worse then you should consult your doctor as you may need further medicines.

Your doctor may tell you to use your nebuliser at a regular time each day or they may tell you to only use it when you are very wheezy or short of breath.

If your doctor has told you to use your nebuliser at regular times each day do not worry if you forget to take a dose at the right time, just inhale the next dose when it is due or before if you become wheezy. Do not take double the dose.

If you accidentally take a larger dose of your Salbutamol Nebuliser Solution than you should, you should tell your doctor as soon as possible. If you take a much larger dose than usual tell your doctor or the nearest hospital casualty department immediately.

4. Possible side effects

Like all medicines, salbutamol can have side effects. If after taking this medicine you immediately experience a worsening of your asthma symptoms then stop using this medicine and contact your doctor immediately.

Other reactions that may occur include:

- Allergic reactions (itchy rash, swelling of the lips, eyes or tongue, collapse i.e. fainting). If these occur you should see your doctor as soon as possible.
- Mouth or throat irritation.
- Palpitations, mild tremor, dizziness, headache.
- Muscle cramps
- Abnormal heart rhythm (e.g. faster than usual)
- Low potassium in your blood
- Hyperactivity in children.

If any side effects are bothering you should see your doctor. If you feel unwell see your doctor or go to the nearest casualty immediately as this medicine may have to be stopped and you may need other treatment.

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

In patients who are also taking anticholinergic medicines (such as ipratropium) it is possible to suffer from an eye condition called glaucoma (increased pressure in the eyes). This can be made worse by allowing the nebuliser mist to get into the eyes. Either a mouthpiece should be used instead of a face mask, or if a face mask is preferred protective eye goggles should be worn.

5. Storing Salbutamol Nebuliser Solution

Keep out of the reach and sight of children.

Do not take after the expiry date on the labelling. Store in the original package, to protect the ampoules from light. The ampoules should be protected from light after removal from the foil over-wrap.

Use the ampoules within 3 months after first opening the foil over-wrap. Make a note of the 'discard by' date in the space provided. Always return the unopened ampoules to the foil over-wrap and place back into the box after use. Return any unused ampoules to your pharmacist for disposal.

6. Further information on how to use your Salbutamol Nebuliser Solution

- Set up the nebuliser as usual and get it ready for filling.
- Open the foil wrapping by cutting along the side. Only open when you are ready to use the first ampoule.
- Take the ampoule strip out of the wrapping and remove the end ampoule by twisting downwards and away from you. Replace the unused ampoules back into the foil over-wrap and place them back into their box.
- To open the ampoule. Hold the body and top of the ampoule securely and then twist the body.
- Carefully place the open end of the ampoule into the nebuliser container and empty the contents by squeezing slowly.
- Set up and use the nebuliser as you have been shown.
- Ensure that any remaining solution left in your nebuliser after use is discarded and your nebuliser is cleaned as recommended.

You must only dilute the contents of the ampoule if you have been told to do so by your doctor. If you have been told to dilute the contents then empty the ampoule into the nebuliser container and add the amount of sterile sodium chloride solution that your doctor has told you to use. Shake gently to mix before using.

Date prepared: September 2005

Remember: this medicine is for you. Only a doctor can prescribe it for you. Never give it to others as it may harm them even if their symptoms are the same as yours.

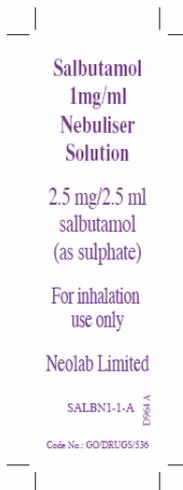
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**SALBUTAMOL 1MG/ML NEBULISER SOLUTION
SALBUTAMOL 2MG/ML NEBULISER SOLUTION**

PL 08137/0083 & 0131

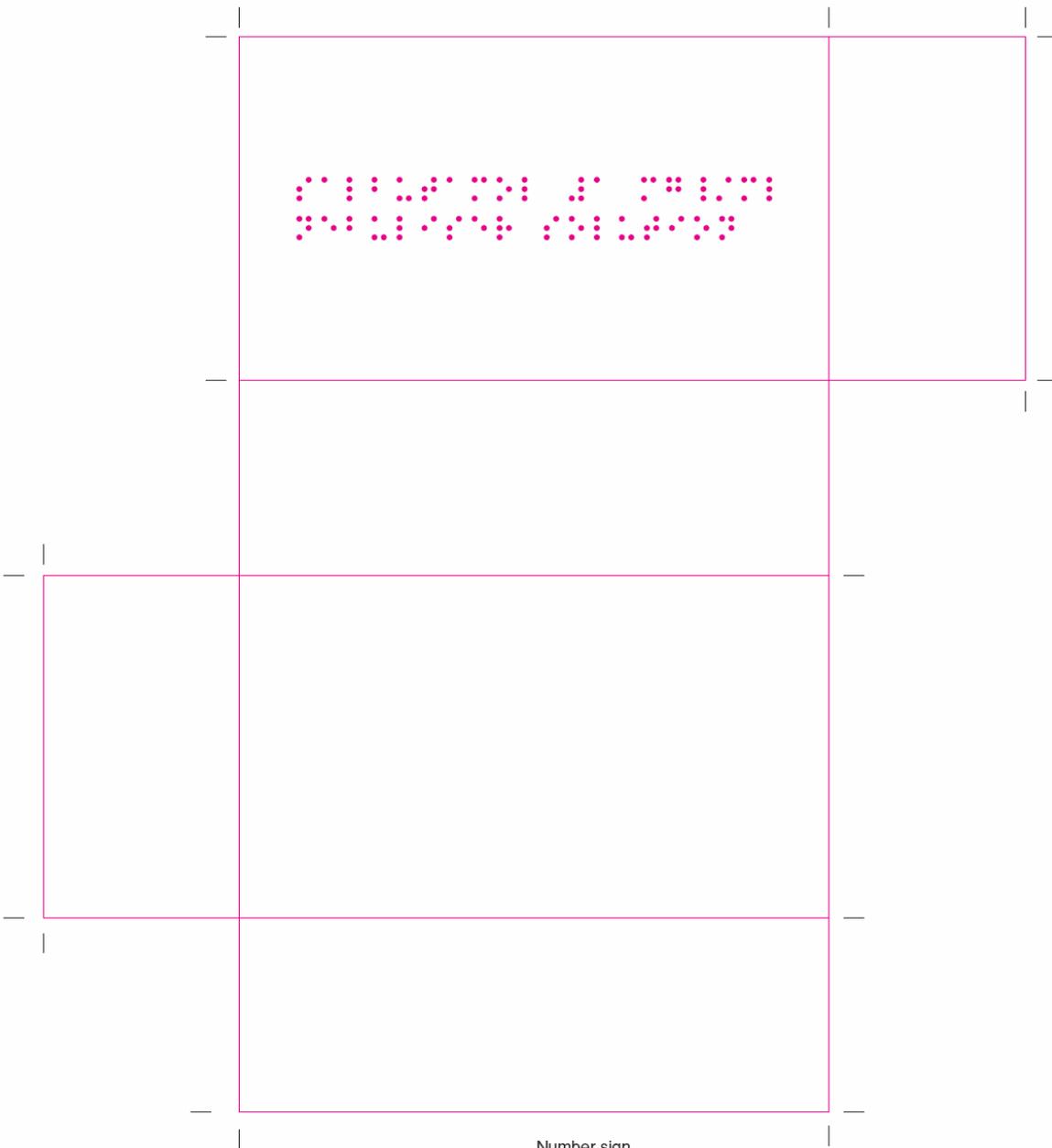
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**Salbutamol 1mg/ml
Nebuliser Solution**

2.5 mg / 2.5 ml ampoule

For inhalation use only

20 ampoules



Salbutamol 1mg/ml Nebuliser Solution

2.5 mg / 2.5 ml ampoule

PL 08137/0083
MA Holder: Neolab Ltd, 57 High Street, Odiham, Hants,
RG29 1LF

20 ampoules

**Salbutamol 1mg/ml
Nebuliser Solution**

2.5 mg / 2.5 ml ampoule

Each nebule contains 2.5mg / 2.5ml salbutamol (as sulphate).
Also includes sodium chloride, sulphuric acid for pH adjustment and water.
Inhale the solution using a nebuliser as directed by your doctor.
Please read the enclosed leaflet carefully before use.

For inhalation use. DO NOT INJECT

Each carton contains
20 ampoules in strips of 5 ampoules



Salbutamol 1mg/ml Nebuliser Solution

2.5 mg / 2.5 ml ampoule

POM

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Store in the original package. The ampoules should be protected from light after removal from the foil over-wrap. Use within 3 months after opening the foil over-wrap.

Code No., LOT & EXP will be inkjet printed white packing

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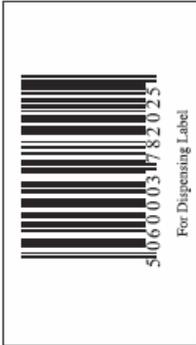
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Salbutamol
2mg/ml
Nebuliser
Solution
5 mg/2.5 ml
salbutamol
(as sulphate)
For inhalation
use only
Neolab Limited
SALBUT-1-A
Code No: 0002055220

Salbutamol
2mg/ml
Nebuliser
Solution
5 mg/2.5 ml
salbutamol
(as sulphate)
For inhalation
use only
Neolab Limited
SALBUT-1-A
Code No: 0002055220
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Cipla PACKAGING DEVELOPMENT

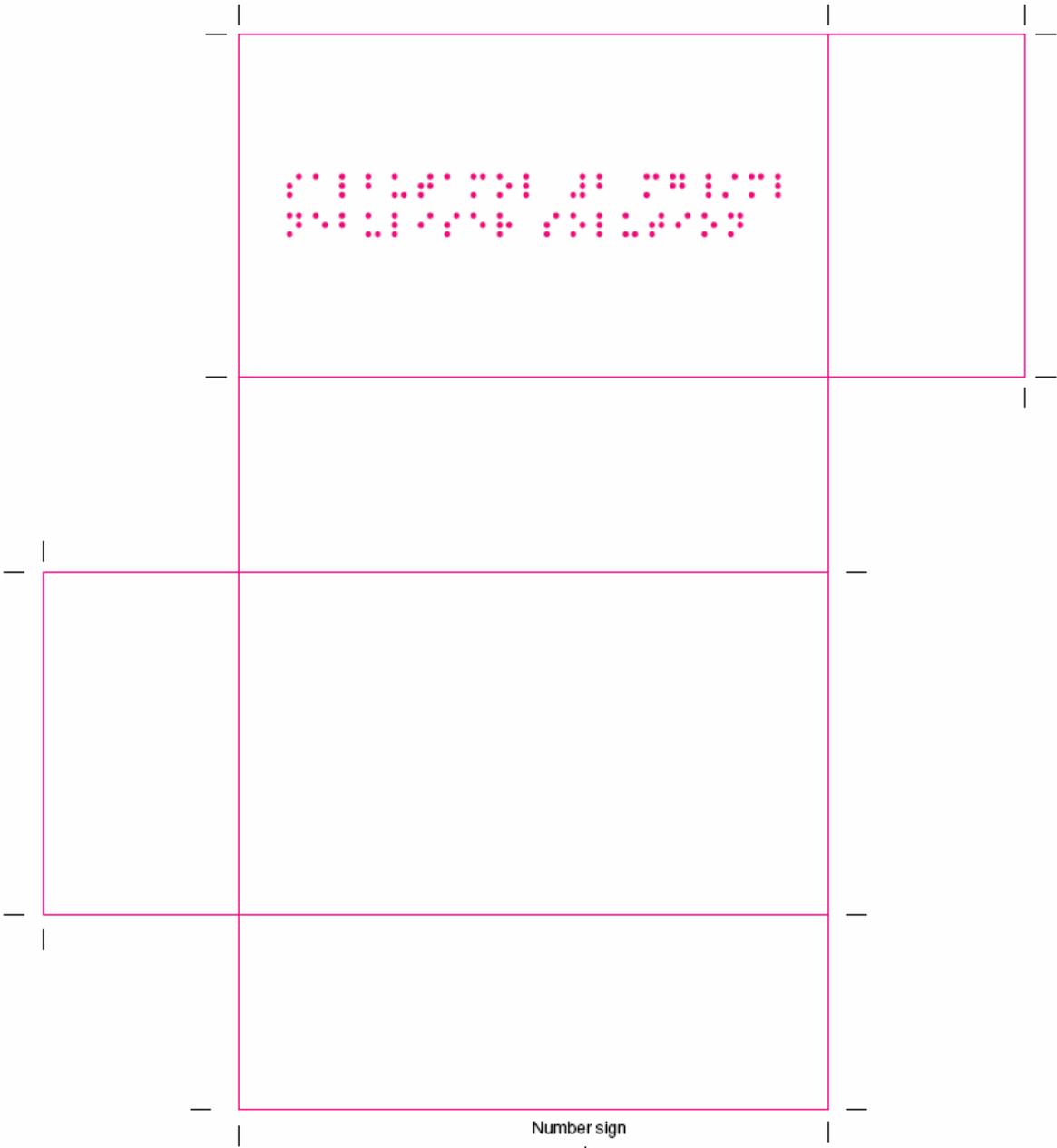
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SALBN2-1C	<h2>Salbutamol 2mg/ml Nebuliser Solution</h2> <p>5 mg / 2.5 ml ampoule</p> <p>For inhalation use only</p> <p>20 ampoules</p> 	Salbutamol 2mg/ml Nebuliser Solution 5 mg / 2.5 ml ampoule 20 ampoules
	<h3>Salbutamol 2mg/ml Nebuliser Solution</h3> <p>5 mg / 2.5 ml ampoule</p> <p>PL 08137/0131 MA Holder: Neolab Ltd, 57 High Street, Odiham, Hants, RG29 1LF</p> <p>20 ampoules</p>	D969 A
	<h3>Salbutamol 2mg/ml Nebuliser Solution</h3> <p>5 mg / 2.5 ml ampoule</p> <p>Each nebule contains 5mg / 2.5ml salbutamol (as sulphate). Also includes sodium chloride, sulphuric acid for pH adjustment and water. Inhale the solution using a nebuliser as directed by your doctor. Please read the enclosed leaflet carefully before use.</p> <div style="border: 1px solid black; padding: 2px; width: fit-content; margin: 0 auto;">For inhalation use. DO NOT INJECT</div> <p>Each carton contains 20 ampoules in strips of 5 ampoules</p>	 <p style="writing-mode: vertical-rl; transform: rotate(180deg);">For Dispensing Label 54060031782025</p>
	<h3>Salbutamol 2mg/ml Nebuliser Solution</h3> <p>5 mg / 2.5 ml ampoule</p> <p>KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.</p> <p>Store in the original package. The ampoules should be protected from light after removal from the foil over-wrap. Use within 3 months after opening the foil over-wrap.</p>	FOM

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Salbutamol 2mg/ml
nebuliser solution

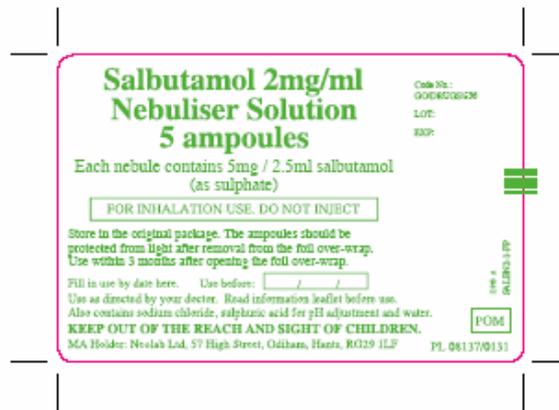
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