

Public Assessment Report
Mutual Recognition Procedure

**BENYLIN MUCUS COUGH MENTHOL FLAVOUR
100 MG/5 ML ORAL SOLUTION**

PROCEDURE NUMBER: UK/H/4651/001/MR

UK PRODUCT LICENCE NUMBER: PL 15513/0165

**BENYLIN MUCUS COUGH MENTHOL FLAVOUR
100 MG/5 ML ORAL SOLUTION
PL 15513/0165**

LAY SUMMARY

On 5th May 2010, the MHRA granted McNeil Products Limited Marketing Authorisations (licences) for Benylin Mucus Cough Menthol flavour 100mg/5ml Syrup (PL 15513/0165).

Benylin Mucus Cough Menthol flavour 100mg/5ml Syrup contains guaifenesin, which belongs to a group of medicines called expectorants. It helps to relieve chesty (productive) coughs by loosening mucus (phlegm), making it easier to cough up and the cough more productive.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Benylin Mucus Cough Menthol flavour 100mg/5ml Syrup outweigh the risks; hence a Marketing Authorisation has been granted.

Please note that the product name was changed after a subsequent mutual recognition procedure to Benylin Mucus Cough Menthol flavour 100mg/5ml Oral Solution. This is the name that will be given for this product in the rest of this Public Assessment Report.

**BENYLIN MUCUS COUGH MENTHOL FLAVOUR
100 MG/5 ML ORAL SOLUTION
PL 15513/0165**

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Module 1

Product Name	Benylin Mucus Cough Menthol flavour 100mg/5ml Oral Solution
Type of Application	Well-established use, Article 10a
Active Substance	Guaifenesin
Form	Oral Solution
Strength	100mg/5ml
MA Holder	McNeil Products Limited, Foundation Park, Roxborough Way, Maidenhead, Berkshire, SL6 3UG, UK
Reference Member State (RMS)	UK
Concerned Member States (CMS)	Belgium, Bulgaria, Cyprus, Czech Republic, Estonia, Greece, Ireland, Italy, Latvia, Lithuania, Luxembourg, Poland, Portugal, Romania, Slovenia, Slovak Republic, Spain
Procedure Number	UK/H/4651/001/DC
Timetable	Day 90 – 7 th September 2011

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Benylin Mucus Cough Menthol flavour 100 mg/5 ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

This product contains 20 mg guaifenesin in each ml (100mg in 5ml).

Each ml also contains:

Ethanol 39.7mg

Ponceau 4R (E124) 0.05mg

Sodium 1.8mg

Glucose

Fructose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution

Clear to slightly opalescent red liquid

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This product is indicated to help loosen phlegm and thin bronchial secretions associated with productive cough, for use in adults and adolescents over 12 years.

4.2 Posology and method of administration

Adults and adolescents over 12 years:

For oral administration: 10 ml (200mg guaifenesin) 4 times a day.

Maximum daily dose: 40ml (800mg guaifenesin)

Children under 12 years:

Not recommended.

The Elderly:

As for adults.

Hepatic/renal dysfunction

Caution should be exercised in severe hepatic and severe renal impairment.

If cough persists for more than 7 days, tends to recur, or is accompanied by a fever, rash, or persistent headache, a physician should be consulted.

4.3 Contraindications

This product is contraindicated in individuals with known hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

This product should not be used for persistent or chronic cough, such as occurs with asthma, or where cough is accompanied by excessive secretions, unless directed by a physician.

A persistent cough may be a sign of a serious condition. If cough persists for more than 7 days, tends to recur, or is accompanied by a fever, rash, or persistent headache, a physician should be consulted.

Caution should be exercised when using the product in the presence of severe renal or severe hepatic impairment.

The concomitant use of cough suppressants is not recommended.

Patients with rare hereditary problems of fructose intolerance or glucose galactose malabsorption should not take this medicine.

This product contains 4.7 vol % ethanol (alcohol), i.e. up to 400 mg per dose, equivalent to approximately 10 ml beer, 4 ml wine per 10 ml dose. This can be harmful for those suffering from alcoholism. The ethanol content should be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver or kidney disease or epilepsy.

This product contains Ponceau 4R (E124) red colouring which may cause allergic reactions.

This product contains 17.6mg sodium per 10ml dose. This should be taken into consideration by those on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

If urine is collected within 24 hours of a dose of this product a metabolite of guaifenesin may cause a colour interference with laboratory determinations of urinary 5-hydroxyindoleacetic acid (5-HIAA) and vanillylmandelic acid (VMA).

Expectorants such as guaifenesin should not be combined with cough suppressants in the treatment of cough since the combination is illogical and patients may be exposed to unnecessary adverse effects.

4.6 Fertility, pregnancy and lactation

Insufficient information is available on the effects of administration of this product during human pregnancy. This product should not be used during pregnancy unless the potential benefit of treatment to the mother outweighs the possible risks to the developing foetus.

It is not certain whether guaifenesin is excreted in breast milk.

4.7 Effects on ability to drive and use machines

Based on its pharmacodynamic profile, guaifenesin has no influence on the ability to drive or use machines.

4.8 Undesirable effects

The following side effects may be associated with the use of guaifenesin:

Immune System Disorders: Hypersensitivity reactions (frequency – not known).

Gastrointestinal disorders: Gastrointestinal discomfort, nausea, vomiting (frequency – not known).

4.9 Overdose

Symptoms and signs

The symptoms and signs of overdose may include gastro-intestinal discomfort, nausea and drowsiness.

Treatment

Treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: R05CA03; Pharmacotherapeutic Group: Cough and Cold Preparations, Expectorants

Guaifenesin is thought to exert its pharmacological action by stimulating receptors in the gastric mucosa. This increases the output from secretory glands of the gastrointestinal system and reflexly increases the flow of fluids from glands lining the respiratory tract. The result is an increase in volume and decrease in viscosity of bronchial secretions. Other actions may include stimulating vagal nerve endings in bronchial secretory glands and stimulating certain centres in the brain, which in turn enhance respiratory fluid flow. Guaifenesin produces its expectorant action within 24 hours.

5.2 Pharmacokinetic properties

Absorption

Guaifenesin is well absorbed from the gastro-intestinal tract following oral administration, although limited information is available on its pharmacokinetics. After the administration of 600 mg

guaifenesin to healthy adult volunteers, the C_{max} was approximately 1.4 ug/ml, with t_{max} occurring approximately 15 minutes after drug administration.

Distribution

No information is available on the distribution of guaifenesin in humans.

Metabolism and elimination

Guaifenesin appears to undergo both oxidation and demethylation. Following an oral dose of 600 mg guaifenesin to 3 healthy male volunteers, the t_{1/2} was approximately 1 hour and the drug was not detectable in the blood after approximately 8 hours.

5.3 Preclinical safety data**Carcinogenicity**

There is insufficient information available to determine whether guaifenesin has carcinogenic potential.

Mutagenicity

There is insufficient information available to determine whether guaifenesin has mutagenic potential.

Teratogenicity

There is insufficient information available to determine whether guaifenesin has teratogenic potential.

Fertility

There is insufficient information available to determine whether guaifenesin has the potential to impair fertility.

6 PHARMACEUTICAL PARTICULARS**6.1 List of excipients**

Xanthan gum
Sodium chloride
Saccharin sodium
Ammonium glycyrrhizate
Sodium benzoate (E211)
Citric acid anhydrous
Sodium citrate
Macrogol glycerol hydroxystearate 40
Levomenthol
Raspberry flavour F2126 (includes ethanol, glucose and fructose)
Caramel (E150) (includes glucose)
Ponceau 4R (E124)
Glycerol
Macrogol 1500
Propylene glycol
Ethanol 96%
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years
In-use: 4 weeks

6.4 Special precautions for storage

Do not store above 25°C
Store in the original container to protect from light

6.5 Nature and contents of container

Type III, Amber glass bottle, containing 150ml, fitted with:

A plastic child resistant cap fitted with a PET-faced wad.

6.6 Special precautions for disposal

No special requirements.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required (these should be disposed of in line with local requirements). These measures will help to protect the environment.

7 MARKETING AUTHORISATION HOLDER

McNeil Products Limited
Foundation Park
Roxborough Way
Maidenhead
Berkshire
SL6 3UG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 15513/0165

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/05/2010

10 DATE OF REVISION OF THE TEXT

24/01/2012

Module 3



- Read all of this leaflet carefully because it contains important information for you. This medicine is available without prescription. However, you still need to use it carefully to get the best results from it.
- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- Contact a doctor if your symptoms worsen or do not improve within 7 days.
- If any of the side-effects gets serious, or if you notice any side-effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What the medicine is and what it is used for.
2. Before you take this medicine.
3. How to take this medicine.
4. Possible side effects.
5. How to store this medicine.
6. Further information.

1 What the medicine is and what it is used for

Benylin Mucus Cough Menthol flavour 100 mg/5 ml oral solution contains guaifenesin which is a type of medicine called an expectorant. It helps to relieve chesty (productive) coughs by loosening phlegm (mucus), making it easier to cough up and the cough more productive.

The medicine is for use in adults and adolescents aged 12 years and over.

2 Before you take this medicine

X Do NOT take this medicine if you

- are allergic (hypersensitive) to guaifenesin or any of the other ingredients (see Section 6 and Section 2).

! Take special care with this medicine

Talk with your doctor or pharmacist before taking this medicine if you:

- have had a cough for more than 7 days or your cough recurs or is accompanied by a fever, rash or persistent headache.
- have a persistent cough that may be caused by asthma.
- have a cough which brings up a lot of mucus (phlegm).
- suffer from liver or kidney problems.
- are taking alcohol.

! Interference with laboratory tests

If you are undergoing urine tests it is important to tell the doctor or nurse you are taking, or have recently taken, this medicine as it can affect some results.

! Taking other medicines

Always tell your doctor or pharmacist if you are taking, or have recently taken, any other medicine, including medicines obtained without a prescription.

- It is not recommended that you take this medicine with other cough medicines intended to stop you from coughing (antitussives or cough suppressants) as they may interfere with the action of this medicine.

! Taking with food or drink

You can take this medicine with or without food or drink.

! Pregnancy and breast-feeding

- If you are pregnant or think you may be pregnant, tell your doctor or pharmacist. This medicine

should not be used during pregnancy unless advised by a doctor.

- Do not take this medicine if you are breast-feeding until you speak with a doctor or pharmacist.

! Driving and using machines

Benylin Mucus Cough Menthol flavour 100 mg/5 ml oral solution is not expected to affect your ability to drive or operate machinery. However, if you do feel unwell, do not drive or use machinery.

! Important information on some of the other ingredients in this medicine

- 4.7 vol % ethanol (alcohol), i.e. up to 400 mg per dose, equivalent to approximately 10 ml beer; 4 ml wine per 10 ml dose. This can be harmful for those suffering from alcoholism. The ethanol content should be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver or kidney disease or epilepsy.
- Ponceau 4R (E124) - red colouring - may cause allergic reactions.
- 17.6 mg sodium per 10 ml dose. This should be taken into consideration by those on a controlled sodium diet.
- Glucose and fructose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3 How to take this medicine

Always take this medicine exactly as described in this leaflet or as your pharmacist has told you. You should check with your doctor or pharmacist if you are not sure.

- This solution is for oral use only.
- Do not use more than the stated dose shown.

turn over ►

Age	Dose
Adults and adolescents over 12 years	Take two 5 ml spoonfuls (total of 10 ml) 4 times a day
Elderly	As for adults
Children under 12 years	Do not give
Patients with liver or kidney problems	Speak to a doctor or pharmacist

- Do **NOT** take more than 4 doses (40 ml) in 24 hours.
- Contact a doctor if your symptoms worsen or do not improve within 7 days.

! If you take too much of this medicine

If anyone has too much, contact a doctor or your nearest Accident and Emergency Department taking this leaflet and pack with you.

Symptoms may include:

- Upset stomach, nausea and drowsiness.

! If you forget to take this medicine

You should only take this medicine as required following the dosage instructions carefully. If you forget to take a dose, take the next dose when needed. **Do not** take a double dose to make up for the forgotten dose. **Do not** take more than 4 doses (40 ml) in 24 hours.

4 Possible side-effects

Like all medicines, Benylin Mucus Cough Menthol flavour 100 mg/5 ml oral solution can cause side-effects, although not everybody gets them.

If you experience any of the following **STOP** using the medicine and seek medical help immediately:

- **Allergic reactions** including skin rashes (which may be severe and include blistering and peeling of the skin) and **itching**.

Mild effects that may occur include:

- Nausea or vomiting.
- Upset stomach.

If any of the side-effects gets serious or if you notice any side-effects not listed in this leaflet, please tell your doctor or pharmacist.

5 How to store this medicine

- Keep this medicine out of the reach and sight of children.
- Do not store this medicine above 25°C.
- Keep the product in the original packaging (bottle in a carton) to protect from light. Do not use if bottle seal is broken when purchased.
- Do not use this medicine after the expiry date which is stated on the bottle and outer carton after 'EXP'. The expiry date refers to the last day of that month.
- Use within 4 weeks of opening.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 Further information

What Benylin Mucus Cough Menthol flavour 100 mg/5 ml oral solution contains:

The active substance is guaifenesin. Each ml of oral solution contains 20 mg of guaifenesin. Each 10 ml of oral solution contains 200 mg of guaifenesin.

Other ingredients: Xanthan gum, sodium chloride, saccharin sodium, ammonium glycyrrhizate, citric acid, sodium citrate, macrogol glycerol hydroxystearate 40, levomenthol, raspberry flavour (includes ethanol, glucose and fructose), glycerol, macrogol 1500, propylene glycol, ethanol, purified water, sodium benzoate (E211), Ponceau 4R (E124), caramel (E150)(includes glucose).

(for further information on some of the ingredients see Section 2).

What Benylin Mucus Cough Menthol flavour 100 mg/5 ml oral solution looks like and contents of the pack

Benylin Mucus Cough Menthol flavour 100 mg/5 ml oral solution is a clear to slightly opalescent red solution for oral use only. It is available in a 150 ml brown glass bottle fitted with a plastic child resistant cap.

Marketing authorisation holder: McNeil Products Ltd, Maidenhead, Berkshire, SL6 3UG, UK.

Manufacturer: Famar Orléans, 5 avenue de Concyr, 45071 Orleans, Cedex 2, France.

This package leaflet was prepared November 2011.

Benylin is a registered trade mark.



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Module 4 Labelling

Benylin®

**MUCUS
COUGH
MENTHOL
FLAVOUR**

**100 mg/5 ml
Oral Solution**

Guaifenesin

Helps to relieve chesty (productive) coughs by loosening phlegm, making it easier to cough up.

DOSE: For oral use only. Adults and adolescents aged 12 years and over:
Two 5 ml spoonfuls 4 times a day.
Do not use in children under 12 years. Do not use more than 4 doses in 24 hours. Do not exceed the stated dose.
As with all similar medicines, if you are pregnant or breast-feeding, consult your doctor or pharmacist before taking this product.
Please consult your doctor or pharmacist if symptoms persist for more than 7 days.

CONTENTS Each ml of oral solution contains: Guaifenesin 20 mg (100 mg in 5 ml). Also contains: Ethanol, glucose, fructose, Ponceau 4R (E124) and sodium. (See leaflet for further information). Contains menthol flavour.

Read the package leaflet before use.
Do not store above 25 °C. Store in the original container to protect from light. Do not use if bottle seal is broken when purchased. Use within 4 weeks of opening. Keep out of the reach and sight of children.

Marketing Authorisation holder: McNeil Products Ltd, Maidenhead, Berkshire, SL6 3UG, UK.

McNeil
Products Ltd.

150 ml e

LOT

EXP

F308663-11-0311

PL 15513/0165

LOT

EXP

6typesR

mm/yyyy



Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, Belgium, Bulgaria, Cyprus, Czech Republic, Estonia, Greece, Ireland, Italy, Latvia, Lithuania, Luxembourg, Poland, Portugal, Romania, Slovenia, Slovak Republic and Spain agreed to grant Marketing Authorisations to McNeil Products Limited for the product Benylin Mucus Cough Menthol flavour 100mg/5ml Oral Solution on 7th September 2011. This was a mutual recognition procedure with the UK as RMS and Belgium, Bulgaria, Cyprus, Czech Republic, Estonia, Greece, Ireland, Italy, Latvia, Lithuania, Luxembourg, Poland, Portugal, Romania, Slovenia, Slovak Republic and Spain as concerned member states (UK/H/4659/001/MR). Previously, the UK had granted a Marketing Authorisation for the medicinal product Benylin Mucus Cough Menthol flavour 100mg/5ml Syrup (PL 15513/0165) to McNeil Products Limited on 5th May 2010.

This product has a general sales licence (GSL) and is not subject to medical prescription. This product is indicated to help loosen phlegm and thin bronchial secretions associated with productive cough, for use in adults and adolescents over 12 years.

This application for Benylin Mucus Cough Menthol flavour 100mg/5ml Oral Solution is submitted as a well-established use application, according to Article 10a of Directive 2001/83/EC.

Expectorants are defined as drugs which augment the output of respiratory tract fluid. They are used for cough induced by irritation due to insufficient demulcent action of the respiratory tract fluid below the epiglottis. The use of an expectorant is recommended for symptomatic relief in productive chesty coughs where phlegm persists, helping to loosen and remove it from the airways. A demulcent is an agent that forms a soothing film on the surface of mucous membranes and thereby demulcents can relieve irritation due to inflamed or irritated mucous membranes.

The Marketing Authorisation Holder has provided the following justification for not submitting an Environmental Risk Assessment:

'The applicant advises that an environmental risk assessment according to CPMP guideline CPMP/SWP/4447/00 (Note for Guidance on the Environmental Risk Assessment of Medicinal Products for Human Use) has not been provided.'

The active substance, guaifenesin, has been registered in medicinal products in the UK and throughout the European Union for many years and is used in the treatment of cough. The addition of this product is not expected to lead to a significant increase in available guaifenesin. Therefore, it is concluded that there are no potential risks presented by the medicinal product for the environment.'

No new non-clinical and clinical efficacy studies were conducted for this bibliographic application, which is acceptable given that guaifenesin is a widely used, well-known substance.

To support the application, the applicant has submitted a review based on literature.

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product at all sites responsible for the manufacture and assembly of this product prior to granting the National Marketing Authorisation.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Benylin Mucus Cough Menthol flavour 100mg/5ml Oral Solution
Name(s) of the active substance(s) (INN)	Guaifenesin
Pharmacotherapeutic classification (ATC code)	Expectorants (R05CA)
Pharmaceutical form and strength(s)	100 mg/5 ml oral solution
Reference numbers for the Mutual Recognition Procedure	UK/H/4651/001/MR
Reference Member State	United Kingdom
Member States concerned	Belgium, Bulgaria, Cyprus, Czech Republic, Estonia, Greece, Ireland, Italy, Latvia, Lithuania, Luxembourg, Poland, Portugal, Romania, Slovenia, Slovak Republic, Spain
Marketing Authorisation Number(s)	PL 15513/0165
Name and address of the authorisation holder	McNeil Products Limited, Foundation Park, Roxborough Way, Maidenhead, Berkshire, SL6 3UG, UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

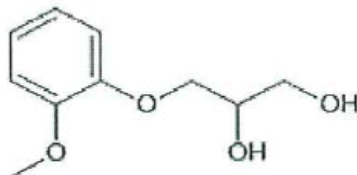
III.1 QUALITY ASPECTS

DRUG SUBSTANCE

Guaifenesin

INN: Guaifenesin
Chemical name: 3-(2-methoxyphenoxy)-1,2-propanediol

Structure:



Physical form: A white or grey crystalline powder with a slightly bitter aromatic taste
Solubility: Soluble in water, freely soluble in ethanol
Molecular formula: $C_{10}H_{14}O_4$
Molecular weight: 198.21

An appropriate specification based on the European Pharmacopoeia has been provided.

All aspects of the manufacture of the active substance guaifenesin from its starting materials are controlled by a Certificate of Suitability or an Active Substance Manufacturing File (ASMF).

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

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient.

An appropriate specification is provided for the active substance etoricoxib. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and certificates of analysis have been provided all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

An appropriate retest period has been proposed based on stability data submitted for the active substance guaifenesin.

DRUG PRODUCT

Other ingredients

Other ingredients consist of excipients Xanthan gum, sodium chloride, saccharin sodium, ammonium glycyrrhizate, sodium benzoate (E211), citric acid anhydrous, sodium citrate, macrogol glycerol hydroxystearate 40, levomenthol, raspberry flavour F2126 (includes ethanol, glucose and fructose), caramel (E150) (includes glucose), ponceau 4R (E124), glycerol, macrogol 1500, propylene glycol, ethanol 96% and purified water

All excipients with the exception of ponceau 4R (E124), caramel (E150) and raspberry flavour F2126 (includes ethanol, glucose and fructose) comply with their relevant European Pharmacopoeia monographs. Ponceau 4R (E124), caramel (E150) and raspberry flavour F2126 (includes ethanol, glucose and fructose) comply with in-house specifications.

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

Product development

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid.

Manufacture

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

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

Finished product specification

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

Container-Closure System

The product is packaged in Type III amber glass bottles with plastic child resistant cap fitted with a PET-faced wad.

Specifications and certificates of analysis for the packaging types used have been provided. All primary product packaging complies with EU legislation regarding contact with food. The product is packaged in one size of 150ml.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years for an unopened product and 4 weeks after it has been opened have been set. This product's storage conditions "Do not store above 25°C" and "Store in the original container to protect from light" are satisfactory.

ADMINISTRATIVE

Expert Report

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

Summary of Product Characteristics (SPC)

These are pharmaceutically satisfactory.

Labelling

These are pharmaceutically satisfactory.

Patient Information Leaflet (PIL)

This is pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Form

These are pharmaceutically satisfactory.

Conclusion

It is recommended that Marketing Authorisations are granted for these applications.

III.2 PRE-CLINICAL ASPECTS

This application for Benylin Mucus Cough Menthol 100mg/5ml Oral Solution are submitted as abridged bibliographic applications according to Article 10.a of Directive 2001/83/EC.

Guaifenesin has been in clinical use for many years and is a well established substance, therefore no new preclinical data have been supplied with this application and none are required.

III.3 CLINICAL ASPECTS

INTRODUCTION

Type of application

This is an abridged complex national application submitted under article 10(a) of directive 2001/83/EC as amended, a so called "well established use" application. The proposed product is an oral solution containing 100 mg of guaifenesin per 5 ml. Guaifenesin is contained in the following UK marketed products:

Actives	Product Name	MA Number
Guaifenesin 100.0 Pseudoephedrine Hydrochloride 30.0 mg Triprolidine Hydrochloride 1.25 mg	Multi-Action Actifed Chesty Coughs	15513/0011
Guaifenesin 100.0 MG Levomenthol 1.100 MG	Benylin Chesty Coughs Non Drowsy	15513/0056
Guaifenesin 50.000 mg	Benylin Children's Chesty Coughs/Calcough Chesty	15513/0052
Pseudoephedrine Hydrochloride 30.000 mg Guaifenesin 100.000 mg	Non Drowsy Sudafed Expectorant / Benylin Dual Action Chesty Cough and Congestion	15513/0022

These product licences were all registered/granted in 1997.

Clinical Background

Coughing is the body's reflex action to stimulation of sensory nerves in the lining of the respiratory passages and it usually indicates the presence of something that requires removal. As a symptom of the common cold, acute coughing is often provoked as a response to remove excessive viscous phlegm. Coughing is more efficient when preceded by a full intake of air and for this reason poor coordination of airway closure and re-opening may result in a poor cough reflex and an inability to remove excessive phlegm. Ineffective clearance of the airway can potentially lead to development of a chest infection (Pillinger, 2007).

Expectorants are defined as drugs which augment the output of respiratory tract fluid. They are used for cough induced by irritation due to insufficient demulcent action of the respiratory tract fluid below the epiglottis (Boyd, 1954). The use of an expectorant is recommended for symptomatic relief in productive chesty coughs where phlegm persists, helping to loosen and remove it from the airways (Pillinger, 2007). A demulcent is an agent that forms a soothing film on the surface of mucous membranes and thereby demulcents can relieve irritation due to inflamed or irritated mucous membranes (MedicineNet, Inc 2007).

Legal Status

Not subject to medical subscription.

CLINICAL PHARMACOLOGY**Pharmacokinetics****Introduction and overview**

Guaifenesin is readily absorbed from the gastrointestinal tract following oral administration, metabolised, and then excreted in the urine (Micromedex, 2006; Martindale, 2006). It is thought that guaifenesin is metabolised by both oxidation and demethylation (Vandenheuvall et al, 1972; Kauert et al, 1980).

Maynard and Bruce (1978) conducted a single oral dose pharmacokinetic study in 3 normal fasting volunteers. Peak plasma concentrations of approximately 1.4 micrograms/ml occurred 15 minutes after administration of 600mg oral liquid dose of guaifenesin. The half-life was approximately 1 hour and there was no detectable drug in the blood after approximately 8 hours, indicating rapid metabolism and excretion.

The usual oral dose of guaifenesin when used as an expectorant is 200mg to 400mg every four hours to a maximum recommended dose of 2.4g/day (Micromedex, 2006).

Benylin Mucus Cough Menthol 100mg/5ml Oral Solution contains 100mg guaifenesin per 5ml spoonful. The recommended dose for adults and children over 12 years is 10mls (200mg) four times daily (total daily dose: 800mg guaifenesin).

Drug-drug interactions

Guaifenesin or its metabolites are thought to cause colour interference with the urinary determination of vanillylmandelic acid (VMA) leading to a false positive result in a VMA test for catechols (Micromedex, 2006). Similarly urinary determinations of hydroxyindoleacetic acid (5-HIAA) may be falsely increased when nitrosonaphthol reagent is used because of colour interference by guaifenesin metabolites. A warning that this may occur is included in Section 4.5 of the proposed Summary of Product Characteristics (SPC).

Guaifenesin has been in clinical use for years with an established safety and efficacy profile.

PHARMACODYNAMICS

Introduction

No new pharmacodynamic studies were submitted with this application. An overview of the pharmacodynamic profile of guaifenesin is presented in the clinical overview.

A summary is presented below:

Guaifenesin is the glycerol ether of guaiacol and exerts its expectorant action by irritating the gastric mucosa and stimulating respiratory tract secretions. By increasing fluid in respiratory secretions the volume is increased, viscosity is decreased thus making it easier to remove by coughing (Micromedex, 2006). Yuta and Baraniuk (2005) reviewed the mechanism of action of treatments aimed at mucus hypersecretion and concluded that expectorants such as guaifenesin may act as irritants to gastric vagal receptors to evoke efferent parasympathetic reflexes that cause glandular exocytosis of a less viscous mucus mixture. Although guaifenesin has no mucolytic action it may decrease the surface tension of bronchial sputum. When cough is provoked by expectorants, the combined result is to flush tenacious, congealed mucopurulent material from obstructed small airways to lead to a temporary improvement in dyspnoea or the work of breathing.

Dicpinigaitis and Gayle (2003) evaluated the effects of guaifenesin on cough reflex sensitivity in a randomised, double blind, placebo controlled trial. On two separate days, 14 subjects with acute viral upper respiratory tract infection and 14 healthy volunteers underwent a capsaicin cough challenge one to two hours after receiving a single 400mg dose of guaifenesin (capsules) or matched placebo. The concentration of capsaicin inducing five or more coughs (C_5) was determined. No effect on cough sensitivity was observed in the healthy subjects but in those with upper respiratory tract infection the mean log C_5 was significantly higher after guaifenesin than after placebo dosing ($p=0.028$). The authors concluded that guaifenesin may inhibit cough reflex sensitivity in patients whose cough receptors are transiently hypersensitive due to the presence of infection and they speculated that this may be due to a peripheral effect where guaifenesin increased sputum volume (by increasing hydration of the respiratory tract) which enables a more effective mucus barrier to shield cough receptors within the respiratory epithelium from the tussive stimulus.

Physiological effects may also be initiated by the physical properties of the formulation used to deliver the active pharmacological ingredient. The majority of cough medicines that facilitate expectoration are formulated in a vehicle (liquid or lozenge) that also provides a demulcent action in the throat when swallowed. For example, the inclusion of glycerol, honey or sugar syrup helps the formulation to coat the pharyngeal mucosa, which may be inflamed from repeated attempts to remove sputum that can be 'felt' in the upper respiratory tract. The inclusion of sapid agents (e.g. sweet tasting, viscous, and bitter tasting ingredients such as citric acid) triggers reflex salivation and may increase secretion of mucus in the airways. Sweet taste and viscous nature of the vehicle are suggested as fundamental properties for cough medicines (Eccles, 2006).

Benylin Mucus Cough Menthol 100mg/5ml Oral Solution is sweetened with saccharin and contains glycerol and xanthan gum (as a thickener) that contribute to the demulcent properties of its vehicle. Benylin Mucus Cough Menthol 100mg/5ml Oral Solution also includes an extra flavouring agent, the volatile oil levomenthol, which provides a cooling sensation when swallowed.

The pharmacodynamic effects of guaifenesin are well recognised. No new studies are considered necessary.

CLINICAL EFFICACY

Introduction

No new efficacy studies were submitted. An overview of published literature was presented in the clinical overview and a summary is presented below:

In 1989 the US Food and Drugs Administration (FDA) review of available over-the-counter expectorant formulations concluded that guaifenesin was an effective expectorant and granted it monograph status (FDA, 1989).

Schroeder and Fahey (2004) reported on a Cochrane Systematic Review to assess the effects of oral over-the-counter (OTC) preparations for acute cough. From their extensive literature search they identified 24 randomised controlled trials comparing oral OTC cough preparations with placebo in children and adults suffering from acute cough in ambulatory settings. Of these only two trials had compared the effects of guaifenesin with placebo. The larger study reported by Robinson et al (1977) used patient questionnaires to rate cough and assess efficacy in 239 adults with acute upper respiratory tract infection. 75% of the 105 participants taking 200mg guaifenesin four times daily stating that the medicine was helpful compared to 31% of the 106 control group ($p < 0.01$). In the second study in 65 adults (mostly university students) with upper respiratory tract infection with cough, Kuhn et al (1982) used tape recordings of cough frequency and a questionnaire of 6 symptoms was used to assess efficacy of 480mg every 6 hours for 30 hours. Cough frequency improved in all the 33 patients in the active treatment group but also improved in 30 of the 32 patients treated with placebo. There were no statistically significant differences between the two groups.

Arroll (2005) also reviewed the evidence supporting the use of guaifenesin identified in the Cochrane Systematic Review. For the two trials that compared guaifenesin with placebo Arroll (2005) calculated the NNTB (number needed to treat for one person to benefit) as 2. The number needed to treat for one person to harm was not reported.

Bolser (2006) searched the National Library of Medicine (PubMed) from 1960 to 2004 for literature relating to the use of antitussive, protussive, or mucolytic agents in humans for the common cold or cough. The authors defined a protussive as an agent that enhances cough effectiveness to promote clearance of airway secretions. Four double blind, placebo-controlled trials of products containing guaifenesin were identified. In addition to the trials by Robinson et al (1977) and Kuhn (1982) in subjects with upper respiratory infection, the authors search also identified two trials in patients with chronic bronchitis (Parvez et al, 1996, and Thomson et al, 1973). The study by Thomson et al (1973) which measured clearance of radio-labelled particles from human lung in subjects with chronic bronchitis failed to demonstrate an effect of guaifenesin on cough frequency.

Parvez et al (1996) conducted a review to evaluate the sensitivity and robustness of methodology to quantify cough and to assess the effectiveness of agents used to ameliorate it. Using data from a series of randomised, double blind, placebo controlled clinical trials in cough due to both chronic bronchopulmonary disease and acute respiratory tract infections, a standardised and validated computerized system for the acquisition and multidimensional analysis of the cough sound was used to quantify cough. Cough count, intensity, latency and total effort expended could then be used as objective measures of efficacy of agents commonly used to relieve coughing. Significant expectorant effects were noted for guaifenesin and bromhexine in patients with productive cough due to chronic bronchopulmonary disease but effects in those with acute respiratory infections could not be demonstrated.

In 1992, Lurie et al highlighted the fact that there is no universally accepted assessment technique to evaluate expectorant drugs. Objective measurement of the ability to expectorate mucus is difficult and evaluation of symptoms using self-reported measure is often imprecise. Lung function tests can only evaluate the possible indirect effects of expectorants, the changes are often minor and do not always correlate with the results from other evaluations. In vitro and ex vivo assessment of bronchial secretions and mucociliary clearance studies whilst providing useful insight cannot replace therapeutic trial data. Lurie et al, 1992, conclude that to be considered efficient, expectorants should not only ease the removal of bronchial secretions but also improve the patient's condition for the duration of treatment. The points made by Lurie et al, 1992, offers a reason why the efficacy of guaifenesin as an expectorant is not documented by well-controlled clinical trials using objective assessments and may help to explain any equivocal results.

The Company has not conducted any specific clinical trials investigating the safety and efficacy of Benylin Mucus Cough Menthol 100mg/5ml Oral Solution. The effective use of guaifenesin to provide symptomatic relief of cough in adults in an ambulatory setting has been established by subjective impression of improvement and by a long history of use.

There is some evidence on the efficacy of guaifenesin. The use of guaifenesin to provide symptomatic relief of chesty coughs is well established. Therefore, no new clinical studies are required.

CLINICAL SAFETY

Introduction

Few undesirable effects have been reported in the literature associated with the use of guaifenesin as an over-the-counter product for the symptomatic relief of chesty cough. It is intended that Benylin Mucus Cough Menthol 100mg/5ml Oral Solution is used for the short-term symptomatic relief of cough. It should not be used for persistent or chronic cough, such as occurs with asthma, or where cough is accompanied by excessive secretions, unless directed by a physician.

Micromedex (2006) lists gastrointestinal discomfort, nausea and vomiting as the most commonly occurring side effects of guaifenesin, and rash, including urticaria, dizziness and headache as having been reported with the its use.

The guaifenesin monograph in Martindale (2006) states that gastrointestinal discomfort, nausea and vomiting have occasionally been reported with guaifenesin, particularly when given in very large doses. The guaifenesin patient information monograph from Medline Plus advises that headache, upset stomach and vomiting may be experienced but to only seek medical advice if the effects are severe or do not go away (Medline Plus, 2007).

A literature search of PubMed and Embase publication databases to identify publications documenting undesirable effects associated with guaifenesin was conducted. No relevant publications containing important new safety findings for guaifenesin were identified.

The Drug Analysis Print (DAP) for guaifenesin (extract period 01 July 1963 -25 May 2006) from the Medicines Control Agency Adverse Drug Reactions Online Information Tracking (ADROIT) system contains 448 spontaneous reports involving 762 reactions associated with the use of guaifenesin. Ninety-three of these reactions were associated with use of guaifenesin as a single constituent but these were scattered across different organ classes with no discernible pattern (Medicines Control Agency, 2006). The DAP contains 5 reactions that

resulted in fatality associated with use of multiconstituent products (1 - fulminant hepatitis, 1 - aplastic anemia, 1 - pneumonia and 2 - congenital disorders) which were most likely due to underlying conditions. As to be expected the data from spontaneous reporting recorded in the DAP is difficult to interpret, however, it does not indicate any serious concerns from the use of guaifenesin as a single active constituent for symptomatic relief of cough.

No company sponsored or non-company sponsored studies of Benylin Mucus Cough Menthol 100mg/5ml Oral Solution have been conducted. However, the Company has previous experience of products containing guaifenesin indicated for symptomatic relief of cough and has marketed a combination product containing the active ingredients guaifenesin (100mg /5ml) and levomenthol since 1997. The latest Periodic Safety Update Report (PSUR) for the combination product (Benylin Chesty Coughs Non-Drowsy) was completed in February 2007 and covered the period from 20 October 2002 to 10 February 2007 (Data on file, 2007). Accumulative distribution data derived from 'units of volume measurement' from Intercontinental Marketing Services (IMS) Global Services indicated that there were 71 million mls of this product distributed from the last quarter of 2002 to the end of the third quarter of 2006. There were no reported fatalities during the reporting period and no changes in the characteristics or frequency of expected reactions. During the PSUR reporting period the Company received one case reporting an unexpected serious adverse event (anaphylactic reaction) and five cases reporting unexpected non-serious adverse events as spontaneous reports. Based on a review of all reported events, no updates to the approved Summary of Product Characteristics (SPC) were indicated. The proposed SPC contains advice that Benylin Mucus Cough Menthol 100mg/5ml Oral Solution is contraindicated in individuals with known hypersensitivity to the product, or any of its components.

Gastro-intestinal discomfort, nausea and vomiting will be listed as side effects on the Summary of Product Characteristics for Benylin Mucus Cough Menthol 100mg/5ml Oral Solution.

Potential for Abuse, Misuse or Dependence

The potential for abuse, misuse or dependence of Benylin Mucus Cough Menthol 100mg/5ml Oral Solution is small because it does not impart a central stimulant action on the CNS. A literature search of PubMed and Embase publication databases to identify publications documenting reports of abuse, misuse, or dependence associated with guaifenesin was conducted. This literature search identified a few reports in the literature that suggest abuse of medications containing guaifenesin may lead to formation of renal calculi. Guaifenesin monographs in Micromedex (2006) and Martindale (2006) refer to two such publications (Pickens et al, 1999 and Assimos et al, 1999).

Pickens et al (1999) found that renal calculi in 11 of 24 patients contained a calcium salt of beta-(2-methoxyphenoxy)-lactic acid, a metabolite of guaifenesin. A similar report by Assimos et al (1999) indicated that renal calculi from 7 patients contained high amounts of the same guaifenesin metabolite. However, patients in both reports were also found to have been using excessive amounts of a variety of over-the-counter products, taken for their stimulant action. Pickens et al (1999) suggested that their observed increase incidence of guaifenesin stones was related to the over consumption of formulations purchased because they contained ephedrine. Four of the 7 patients reported by Assimos et al (1999) admitted to taking 50 to 100 tablets daily of a product containing 200mg guaifenesin and 25mg ephedrine. More recently Whelan and Schwartz (2004) reported a patient with bilateral ureteral calculi composed of a guaifenesin metabolite (determined by infrared spectroscopy). The authors also indicated that the stones were associated with excessive guaifenesin intake related to a current popularity for ephedrine preparations. When questioned a 22-year old

man admitted to taking 6 to 12 of a combined ephedrine and guaifenesin tablet containing formulation, a day. Bennett et al (2004) reviewed reported cases of ephedrine and guaifenesin-induced nephrolithiasis following an increased use of ephedrine and guaifenesin herbal supplements in the United States over the preceding ten years. They concluded that ephedrine and guaifenesin have potential to cause nephrolithiasis in cases of abuse when taken individually or in combination as herbal supplements. Song et al (2005) also report an incidence of renal calculus composed of pseudoephedrine and guaifenesin. Again in this case the patient had a history of abusing over-the-counter allergy medication.

It would therefore appear that the risk of renal calculi is solely dependent on excessive consumption, particularly by those with a history of general abuse of over-the-counter medications and not specifically linked to a liking for abusing or misusing guaifenesin.

Overdose

Wogoman et al (1999) described a case of fatal intoxication from the combined effects of guaifenesin, diphenhydramine and chlorpheniramine. The-48 year old woman was found dead after consuming over-the-counter medications and the manner of her death was determined to be suicide.

Treatment of overdose should be symptomatic and supportive.

Use in pregnancy and lactation

The Reprotox monograph for guaifenesin from Micromedex refers to one report of inguinal hernia associated with guaifenesin exposure during pregnancy and two other studies where no increase in congenital anomalies were identified (Reprotox, 2006). The Teris entry for guaifenesin suggests that there is no risk of teratogenicity to children born after exposure during gestation based on a 'fair' quality and quantity of data on which their risk estimate is based (Teris, 2006).

The latest Periodic Safety Update Report (PSUR) for Benylin Chesty Coughs (Non-Drowsy) (a combination product containing guaifenesin and menthol) referred to two non-serious in utero exposures reported during the period from 20 October 2002 to 10 February 2007 (Data on file, 2007). One case reported abdominal pain but the outcome was unknown and the other reported no adverse event.

Despite the lack of adverse reports associated with the use of guaifenesin during pregnancy, the Company considers that there is insufficient information available on the effects of administration of Benylin Mucus Cough Menthol 100mg/5ml Oral Solution during human pregnancy. It is proposed that the Summary of Product Characteristics (SPC) will advise that Benylin Mucus Cough Menthol 100mg/5ml Oral Solution, like most medicines, should not be used during pregnancy unless the potential benefit of treatment to the mother outweighs the possible risks to the developing foetus.

It is not certain whether guaifenesin is excreted in breast milk and this statement is also included in the proposed SPC.

Guaifenesin has been in clinical use for many years and the safety profile is well recognised.

EXPERT REPORTS

The clinical expert report has been written by a suitably qualified person and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)

This is satisfactory.

LABELLING

These are satisfactory.

APPLICATION FORMS (MAA)

This is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

This is satisfactory.

OVERALL CONCLUSION

Guaifenesin is a well established medicinal product with known efficacy and safety profiles.

The grant of a Marketing Authorisation is recommended for this application.

**IV OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT
QUALITY**

The important quality characteristics of Benylin Mucus Cough Menthol flavour 100mg/5ml Oral Solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required

EFFICACY

Guaifenesin has been used for many years and is a well-established medicinal product with well-known efficacy and safety profiles.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with guaifenesin is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome