Public Assessment Report

UKPAR

Unicough 14 mg/135 mg/1.1 mg in 5 ml Oral Solution

(diphenhydramine hydrochloride, ammonium chloride, levomenthol)

UK Licence No: PL 42459/0001

Infirst Healthcare Limited
LAY SUMMARY
Unicough 14 mg/135 mg/1.1 mg in 5 ml Oral Solution
(diphenhydramine hydrochloride, ammonium chloride, levomenthol)

This is a summary of the Public Assessment Report (PAR) for Unicough 14 mg/135 mg/1.1 mg in 5 ml Oral Solution (PL 42459/0001). This medicinal product will be referred to as Unicough Oral Solution in this summary, for ease of reading.

This summary explains how Unicough Oral Solution was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Unicough Oral Solution.

For practical information about using Unicough Oral Solution, patients should read the package leaflet or contact their doctor or pharmacist.

What is Unicough Oral Solution and what is it used for?
This medicine is the same as Histalix Syrup (PL 00400/0007R), which is already authorised. The company that makes Histalix Syrup, Wallace Manufacturing Chemists Ltd, has agreed that its scientific data can be used as a basis for the grant of an identical licence for Unicough Oral Solution (Infirst Healthcare Limited; PL 42459/0001).

Unicough Oral Solution is used for the symptomatic relief of common coughs (such as dry and/or tickly, or troublesome cough) associated with upper respiratory tract congestion. It may also be used to aid restful sleep.

How is Unicough Oral Solution used?
Unicough Oral Solution is taken orally. This medicine can be obtained from a pharmacy.

The recommended dosage is one to two 5 ml spoonfuls of Unicough Oral Solution every 4 hours. To aid sleep, two 5 ml spoonfuls at bedtime followed by two 5 ml can be taken every 6 hours if needed.

Unicough Oral Solution must not be given to children under 12 years of age.

For further information on how Unicough Oral Solution is used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

How does Unicough Oral Solution work?
Unicough Oral Solution contains the active ingredients diphenhydramine hydrochloride, an antihistamine that possesses antitussive, antihistaminic, and anticholinergic properties and suppresses the urge to cough; ammonium chloride, an expectorant that helps loosen phlegm and catarrh, and levomenthol, which relieves the discomfort of congestion and also provides a cooling effect in the mouth and throat.

What benefits of Unicough Oral Solution have been shown in studies?
Unicough Oral Solution is considered to be identical to the previously authorised Histalix Syrup, with the same benefits and risks. So no new studies have been provided for Unicough Oral Solution but reference is made to the studies for Histalix Syrup.

What are the possible side effects from Unicough Oral Solution?
Like all medicines, this medicine can cause side effects, although not everybody gets them.
For the full list of all side effects reported with Unicough Oral Solution, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

**Why is Unicough Oral Solution approved?**
No new or unexpected safety concerns arose from this application. The MHRA, therefore, considered that the benefits of Unicough Oral Solution outweigh its risks; and the grant of a Marketing Authorisation was recommended.

**What measures are being taken to ensure the safe and effective use of Unicough Oral Solution?**
A Risk Management Plan (RMP) has been developed to ensure that Unicough Oral Solution is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Unicough Oral Solution including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

**Other information about Unicough Oral Solution**
A Marketing Authorisation was granted in the UK on 23rd April 2015.

The full PAR for Unicough Oral Solution follows this summary.

For more information about taking Unicough Oral Solution read the patient information leaflet (PIL), or contact your doctor or pharmacist.

This summary was last updated in September 2015.
TABLE OF CONTENTS

I  Introduction ................................................................. Page 5
II  Quality aspects .......................................................... Page 6
III Non-clinical aspects .................................................... Page 7
IV  Clinical aspects .......................................................... Page 7
V  User consultation .......................................................... Page 8
VI  Overall conclusion, benefit/risk assessment and recommendation .................................................... Page 8

Table of content of the PAR update ..................................... Page 11
I  INTRODUCTION
The Medicines and Healthcare products Regulatory Agency (MHRA) granted Infirst Healthcare Limited a Marketing Authorisation for the medicinal product Unicough 14 mg/135 mg/1.1 mg in 5 ml Oral Solution (PL 42459/0001) on 23rd April 2015. This pharmacy (P) medicine is indicated for the oral symptomatic relief of common coughs (such as dry and/or tickly, or troublesome cough) associated with upper respiratory tract congestion and aids restful sleep.

The product name was discussed at the Committee for Human Medicines (CHM) 15th-16th January 2015. An alternative name was suggested by the Marketing Authorisation Holder and this was accepted.

This application was submitted as an abridged simple application, according to Article 10c of Directive 2001/83/EC, as amended. The applicant has cross-referred to Histalix Syrup, which was first authorised to Wallace Manufacturing Chemists Ltd (PL 00400/0007R) on 30th January 1989.

Diphenhydramine possesses antitussive, antihistaminic, and anticholinergic properties and suppresses the urge to cough. It also dries up secretions in the nose and chest. Experiments have shown that the antitussive effect is discrete from its sedative effect. Taken at night will assist sleeping.

Ammonium chloride is a "Traditional" expectorant.

Menthol provides subjective relief of upper respiratory congestion, it has mild local anaesthetic and cooling effect.

Unicough oral solution is a thick demulcent, which in the buccal cavity and throat forms a soothing film over the mucous membrane. This brings it into contact with the sensitive nerve endings of the throat lining.

No new data were submitted nor were they necessary for this abridged simple application, as the data are identical to those of the previously granted cross-reference product. Data have been provided for the subsequent variations approved for this product licence (see “Table of content of the PAR update” at the end of this PAR).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of this product.
II QUALITY ASPECTS
II.1 Introduction
This is a simple, informed consent application for Unicough 14 mg/135 mg/1.1 mg in 5 ml Oral Solution submitted under Article 10c of Directive 2001/83/EC, as amended. The applicant has cross-referred to Histalix Syrup, which was first authorised to Wallace Manufacturing Chemists Ltd (PL 00400/0007R) on 30th January 1989. The application is considered valid.

II.2. Drug Substances
Drug substance specifications
The proposed drug substance specifications are consistent with the details registered for the cross-reference product.

II.3. Medicinal Product
Name
The proposed product name for this application is Unicough 14 mg/135 mg/1.1 mg in 5 ml Oral Solution. The product has been named in line with current requirements.

Strength, pharmaceutical form, route of administration, container and pack size
Each 5 ml dose of oral solution contains 14.00 mg of diphenhydramine hydrochloride, 135.00 mg of ammonium chloride and 1.10 mg of levomenthol. The route of administration is oral.

The finished product is packed into 150 ml and 300 ml amber glass bottles with polypropylene cap with enhanced polyethylene (EPE)/polyethylene (PE)/aluminium (Al)/polyethylene terephthalate (PET) wad.

The proposed shelf-life is 36 months with a storage condition ‘Store below 25°C’.

The proposed packaging, shelf-life and storage condition are consistent with the details registered for the cross-reference product.

Legal status
This product is supplied through a pharmacy (P).

Marketing Authorisation Holder/Contact Persons/Company
Infirst Healthcare Limited, Central Point, 45 Beech Street, London, EC2Y 8AD, UK.

The Qualified Person (QP) responsible for pharmacovigilance is stated and a satisfactory Curriculum Vitae (CV) has been provided.

Manufacturer
The proposed manufacturing site is consistent with that registered for the cross-reference product and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

Qualitative and quantitative composition
During the initial abridged simple application, the proposed composition was considered consistent with the details registered for the cross-reference product.

Manufacturing process
During the initial abridged simple application, the proposed manufacturing process was consistent with the details registered for the cross-reference product and the maximum batch size was stated.
Finished product/shelf-life specification
During the initial abridged simple application, the proposed finished product specification was in line with the details registered for the cross-reference product.

TSE Compliance
None of the excipients contain materials of animal or human origin. This is consistent with the cross-reference product.

Bioequivalence
No bioequivalence data are required to support this simple abridged application as the proposed product is manufactured to the same formula utilising the same process as the cross-reference product, Histalix Syrup (PL 00400/0007R).

Expert Report
The applicant cross-refers to the data for Histalix Syrup (PL 00400/0007R) to which this application is claimed to be identical. This is acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The data submitted with the application is acceptable. The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS
Introduction
As this is an abridged simple application submitted under Article 10c of Directive 2001/83/EC, as amended, no new non-clinical data have been supplied and none are required.

Environmental Risk Assessment (ERA)
A suitable justification has been provided for not submitting an environmental risk assessment. As the application is an identical version of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

Discussion on the non-clinical aspects
The grant of a Marketing Authorisation is recommended.

IV CLINICAL ASPECTS
Introduction
As this is an abridged simple application submitted under Article 10c of Directive 2001/83/EC, as amended, no new clinical data have been supplied and none are required.

Risk Management Plan (RMP)
The Marketing Authorisation Holder (MAH) has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Unicough 14 mg/135 mg/1.1 mg in 5 ml Oral Solution.
A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>hypersensitivity to any of the ingredients</td>
<td>Inclusion in SmPC, and labelling / patient information leaflet.</td>
<td>None</td>
</tr>
<tr>
<td>use in children below 12 years of age</td>
<td>Inclusion in SmPC, and labelling / patient information leaflet.</td>
<td>None</td>
</tr>
<tr>
<td>use for patients on MAOI therapy within previous 14 days</td>
<td>Inclusion in SmPC, and labelling / patient information leaflet.</td>
<td>None</td>
</tr>
<tr>
<td>combination with other treatments for coughs and colds</td>
<td>Inclusion in SmPC, and labelling / patient information leaflet.</td>
<td>None</td>
</tr>
<tr>
<td>additive CNS depressant effects (e.g. alcohol, barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives and antipsychotics)</td>
<td>Inclusion in SmPC, and labelling / patient information leaflet.</td>
<td>None</td>
</tr>
<tr>
<td>additive anti-muscarinic effects (e.g. atropine and some anti-depressants)</td>
<td>Inclusion in SmPC, and labelling / patient information leaflet.</td>
<td>None</td>
</tr>
<tr>
<td>use in patients with prostatic hypertrophy</td>
<td>Inclusion in SmPC, and labelling / patient information leaflet.</td>
<td>None</td>
</tr>
<tr>
<td>use in patients with urinary retention</td>
<td>Inclusion in SmPC, and labelling / patient information leaflet.</td>
<td>None</td>
</tr>
<tr>
<td>use in patients with susceptibility to ‘closed angle’ glaucoma</td>
<td>Inclusion in SmPC, and labelling / patient information leaflet.</td>
<td>None</td>
</tr>
<tr>
<td>use in patients with hepatic disease.</td>
<td>Inclusion in SmPC, and labelling / patient information leaflet.</td>
<td>None</td>
</tr>
<tr>
<td>use in pregnancy</td>
<td>Inclusion in SmPC, and labelling / patient information leaflet.</td>
<td>None</td>
</tr>
<tr>
<td>use during lactation</td>
<td>Inclusion in SmPC, and labelling / patient information leaflet.</td>
<td>None</td>
</tr>
</tbody>
</table>

**Discussion on the clinical aspects**
The grant of a Marketing Authorisation is recommended.

**V User consultation**
User-testing of the patient information leaflet (PIL) for Unicough 14 mg/135 mg/1.1 mg in 5 ml Oral Solution has been accepted based on the bridging report provided by the applicant making reference to the successful user-testing of the PIL for Histalix Syrup (PL 00400/0007R) as the ‘parent PIL’.

**VI Overall conclusion, benefit/risk assessment and recommendation**
The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. The applicant’s product is identical to the reference product. Extensive clinical experience with diphenhydramine hydrochloride, ammonium chloride and levomenthol is considered to have demonstrated the therapeutic value of the compounds. The benefit-risk assessment is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The Summary of Product Characteristics and Patient Information Leaflet (PIL) are consistent with the details registered for the reference product.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Unicough 14 mg/135 mg/1.1 mg in 5 ml Oral Solution is presented at the end of this PAR (see Annex 1).
Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
</tr>
</thead>
<tbody>
<tr>
<td>To replace raspberry flavour with cocoa flavour and make changes to the manufacturing method.</td>
<td>Type II</td>
<td>Module 3 (excipients, method of manufacture)</td>
<td>24/04/2015</td>
<td>08/05/2015</td>
<td>Approval</td>
<td>No</td>
</tr>
<tr>
<td>To update section 4.1 and 5.1 of the SmPC to modify an approved therapeutic indication - cough. In addition, to update section 4.4 of the SmPC with excipient warnings. Consequently, the PIL and label has been updated.</td>
<td>Type II</td>
<td>SmPC PIL labels</td>
<td>24/04/2015</td>
<td>04/08/2015</td>
<td>Approval</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Annex I

Reference: PL 42459/0001-0004
Product: Unicough 14mg / 135mg / 1.1mg Oral in 5ml Solution
Marketing Authorisation Holder: Infirst Healthcare Limited
Active Ingredients: Diphenhydramine hydrochloride, ammonium chloride, levomenthol
Reason: To update section 4.1 and 5.1 of the SmPC to modify an approved therapeutic indication - cough. In addition, to update section 4.4 of the SmPC with excipient warnings. Consequently, the PIL and label has been updated

Background
The marketing authorisation holder proposes to change the indications from “For the oral symptomatic relief of troublesome cough associated with upper respiratory tract congestion and aids restful sleep” to “For the oral symptomatic relief of common coughs (such as dry and/or tickly, or troublesome cough) associated with respiratory tract congestion and aids restful sleep”.

Supporting Evidence
Revised versions of the Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labels have been submitted.

Assessor’s Comment
The proposed changes to the SmPC and the corresponding changes to the text of the PIL/labels are acceptable.

Conclusion
The grant of this variation is recommended. The current SmPC and PIL are available on the MHRA website. The current labels are provided below.

Decision - Granted
Date - 04 August 2015
Unicough 14 mg/135 mg/1.1 mg in 5 ml Oral Solution

**Effective relief of common coughs**

**Dry and/or Tickly**

Troublesome chesty cough

- Reduces the urge to cough
- Helps prevent sleep disruption

**NEW UNICOUGH**

14 mg / 135 mg / 1.1 mg in 5 ml ORAL SOLUTION

Diphenhydramine hydrochloride
Ammonium chloride
Limonene

Each 5 ml contains:

- Diphenhydramine HCl 14 mg
- Ammonium chloride 135 mg
- Limonene 1.1 mg

Also contains:

- Sucrose, coca flavour, glycerol, propylene glycol, sodium citrate, preservatives (E219, E215, E216 and butyl hydroxybenzoate), and water.

**Warning:**

May cause drowsiness.
Do not drive or operate machinery.
Avoid alcoholic drink.

Product licence holder:

Infinit Healthcare Limited
Central Point, 45 Beach Street
London, EC2Y 9AD, UK

PL 42459/0001

15 mm bleed area
Unicough 14 mg/135 mg/1.1 mg in 5 ml Oral Solution

Each 5ml contains:
- Diphenhydramine HCl 14mg
- Ammonium chloride 135mg
- Levomenthol 1.1mg

Also contains:
- Glycerol, propylene glycol, sodium citrate, preservatives (EDTA, E215, E230 and isobutyl hydroxyanisole), and water.

Effective relief of common coughs

Dry and/or Tickly
Troublesome chesty cough

Reduces the urge to cough
New cocoa formulation
& helps prevent sleep disruption

Storage:
Keep the bottle tightly closed.
Keep out of the sight and reach of children.
Store below 25°C.

Do not use after the expiry date marked on the carton base.

Warning: May cause drowsiness.
Do not drive or operate machinery.
Avoid alcoholic drinks.

Product license holder:
Innfit Healthcare Limited
Central Park, 45 Beach Street,
London, EC1Y 8AD, UK.
PL.42459/0001  D0195-3