Mucodyne-Clear 250 mg/5 ml Syrup

PL 04425/0665

UKPAR

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MUCODYNE-CLEAR 250 MG/5 ML SYRUP

PL 04425/0665

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation (licence) for the medicinal product Mucodyne-Clear 250 mg/5 ml Syrup (product licence number: 04425/0665). This medicine is available only by prescription.

Mucodyne-Clear 250 mg/5 ml Syrup is used for problems with the breathing passages (respiratory tract). These problems happen when too much mucus (phlegm) is made or the mucus is too sticky. Mucodyne-Clear 250 mg/5 ml Syrup works by making mucus less sticky and easier to cough up.

Mucodyne-Clear 250 mg/5 ml Syrup raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.
MUCODYNE-CLEAR 250 MG/5 ML SYRUP

PL 04425/0665

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Mucodyne-Clear 250 mg/5 ml Syrup to Aventis Pharma Limited on 1 February 2010.

This is an abridged application for Mucodyne-Clear 250 mg/5 ml Syrup submitted under Article 10(c) of EC Directive 2001/83, last paragraph. The applicant claims that this product is identical to Mucodyne 250mg/5ml Syrup (PL 04425/0204), which has been licensed since 12 March 1992.

No new data were submitted, nor was it necessary for this simple application, as the data are identical to those for the previously granted cross-reference product.

Mucodyne-Clear 250 mg/5 ml Syrup is a mucolytic agent for the adjunctive therapy of respiratory tract disorders characterised by excessive, viscous mucus, including chronic obstructive airways disease.
PHARMACEUTICAL ASSESSMENT

CARBOCISTEINE
The carbocisteine used in this product complies with the Ph. Eur. monograph and is satisfactory.

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT
A clear amber coloured syrupy liquid containing 250 mg of carbocisteine per 5 ml. The syrup also contains sucrose, ethanol, methyl parahydroxybenzoate (E218) and sodium.
There is no difference between the composition of the proposed product and that of the already licensed cross reference product.

ADDITIONAL DATA REQUIREMENTS
The manufacturing process, finished product specification and active ingredient specification are in line with those for the reference product and are satisfactory.

The applicant has provided TSE declarations from the manufacturers/suppliers of all excipients used in the manufacture of the finished product confirming that none of the materials used are derived from animal products.

EXPERT REPORTS
Satisfactory expert reports in the form of quality, non-clinical and clinical overall summaries are provided, with signed declarations from each expert confirming that the applicant’s product is identical to the reference product in all particulars. Expert CVs are also submitted and are acceptable.

PRODUCT LITERATURE
The proposed SPC, PIL and labels are identical to those for the reference product and are satisfactory. The 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. 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.

No PIL or label mock ups have been provided. In accordance with the medicines legislation, the product shall not be marketed in the UK until prior approval of the product labelling and leaflet mock-ups has been obtained.

ASSESSOR’S OVERALL CONCLUSIONS
A Marketing Authorisation may be granted for this product.
PRECLINICAL ASSESSMENT

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

**OVERVIEW**
A statement has been provided confirming that the clinical particulars for Mucodyne-Clear 250 mg/5 ml Syrup are identical to those for the already licensed product; Mucodyne 250mg/5ml Syrup (PL 04425/0204). This is satisfactory.

**BIOAVAILABILITY AND BIOEQUIVALENCE**
No bioequivalence study has been performed to support this application and none is needed.

**PRODUCT LITERATURE**
All product literature is medically satisfactory.

**ASSESSOR’S OVERALL CONCLUSIONS**
It is recommended that a marketing authorisation can be granted.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
Mucodyne-Clear 250 mg/5 ml Syrup (PL 04425/0665) is identical to the already licensed reference product. This product is, therefore, pharmaceutically satisfactory.

PRECLINICAL
No new preclinical data were submitted and none are required for an application of this type.

EFFICACY
The efficacy of carbocisteine is well established. The SPC, PIL and labelling are satisfactory and consistent with those for the cross-reference product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been shown to be associated with carbocisteine. The risk benefit ratio is therefore considered to be acceptable.
MUCODYNE-CLEAR 250 MG/5 ML SYRUP

PL 04425/0665

STEPS TAKEN FOR ASSESSMENT

<table>
<thead>
<tr>
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<th>The MHRA received the marketing authorisation application on 5 November 2009</th>
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<tbody>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 7 December 2009</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the application was determined on 1 February 2010</td>
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</tbody>
</table>
1 NAME OF THE MEDICINAL PRODUCT
Mucodyne-Clear 250 mg/5 ml Syrup

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 5 ml of oral solution contains 250 mg of Carbocisteine. Also contains 2 g of sucrose, 70 mg of ethanol (1.6% v/v), 7.5 mg of methyl parahydroxybenzoate (E218) and 33 mg of sodium (1.4 mmol).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Syrup

A clear amber coloured syrupy liquid

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Carbocisteine is a mucolytic agent for the adjunctive therapy of respiratory tract disorders characterised by excessive, viscous mucus, including chronic obstructive airways disease.

4.2 Posology and method of administration

Adults including the elderly:
Dosage is based upon an initial daily dosage of 2250 mg Carbocisteine in divided doses, reducing to 1500 mg daily in divided doses when a satisfactory response is obtained e.g. for normal syrup 15ml tds reducing to 10ml tds.

Children:
This formulation is not recommended for children. The normal daily dosage is 20 mg/kg bodyweight in divided doses. It is recommended that this is achieved with Mucodyne Paediatric Syrup.

Mucodyne-Clear Syrup is for oral use.

4.3 Contraindications
Hypersensitivity to the active substance(s) or to any of the excipients.
Use in patients with active peptic ulceration.

4.4 Special warnings and precautions for use
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
4.5 **Interaction with other medicinal products and other forms of interaction**
None stated.

4.6 **Pregnancy and lactation**
Although tests in mammalian species have revealed no teratogenic effects, Mucodyne is not recommended during the first trimester of pregnancy.

Use in lactation: Effects not known.

4.7 **Effects on ability to drive and use machines**
None.

4.8 **Undesirable effects**

- **Immune System Disorders**
  There have been reports of anaphylactic reactions and fixed drug eruption.

- **Gastrointestinal Disorders**
  There have been rare reports of gastrointestinal bleeding occurring during treatment with Mucodyne.

- **Skin and Subcutaneous Tissue Disorders**
  There have been reports of skin rashes and allergic skin eruptions.

4.9 **Overdose**
Gastric lavage may be beneficial, followed by observation. Gastrointestinal disturbance is the most likely symptom of Mucodyne overdosage.

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**
ATC code: R05CB03

Carbocisteine (S-carboxymethyl L-cysteine) has been shown in normal and bronchitic animal models to affect the nature and amount of mucus glycoprotein which is secreted by the respiratory tract. An increase in the acid:neutral glycoprotein ratio of the mucus and a transformation of serous cells to mucus cells is known to be the initial response to irritation and will normally be followed by hypersecretion. The administration of Carbocisteine to animals exposed to irritants indicates that the glycoprotein that is secreted remains normal; administration after exposure indicates that return to the normal state is accelerated. Studies in humans have demonstrated that Carbocisteine reduces goblet cell hyperplasia. Carbocisteine can therefore be demonstrated to have a role in the management of disorders characterised by abnormal mucus.

5.2 **Pharmacokinetic properties**
Carbocisteine is rapidly absorbed from the GI tract. In an ‘in-house’ study, at steady state (7 days) Mucodyne capsules 375mg given as 2 capsules t.d.s. to healthy volunteers gave the following pharmacokinetic parameters:
### Plasma Determinations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>T Max (Hr)</td>
<td>2.0</td>
<td>1.0-3.0</td>
</tr>
<tr>
<td>T½ (Hr)</td>
<td>1.87</td>
<td>1.4-2.5</td>
</tr>
<tr>
<td>KEL (Hr⁻¹)</td>
<td>0.387</td>
<td>0.28-0.50</td>
</tr>
<tr>
<td>AUC_{0-7.5} (mcg.Hr.ml⁻¹)</td>
<td>39.26</td>
<td>26.0-62.4</td>
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</table>

### Derived Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>*CL_{S} (L.Hr⁻¹)</td>
<td>20.2</td>
</tr>
<tr>
<td>CL_{S} (ml.min⁻¹)</td>
<td>331</td>
</tr>
<tr>
<td>V_{D} (L)</td>
<td>105.2</td>
</tr>
<tr>
<td>V_{D} (L.Kg⁻¹)</td>
<td>1/75</td>
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</table>

*Calculated from dose for day 7 of study

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5.3 **Preclinical safety data**

There are no preclinical data of relevance to the prescriber, which are additional to those already included in other section of the SmPC.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**

Methyl parahydroxybenzoate (E218),
Sucrose,
Caramel powder (E150),
Aromatic Elixir (containing ethyl alcohol, rum and aromatic rum flavour),
Cinnamon oil,
Sodium hydroxide,
Purified water.

6.2 **Incompatibilities**

Mixture with linctus of pholcodine causes precipitation of carbocisteine from solution.

6.3 **Shelf life**

36 months.

6.4 **Special precautions for storage**

Store below 25°C.

6.5 **Nature and contents of container**

300ml clear glass bottle (Type III glass) and a polypropylene cap with polyethylene liner together with a graduated polypropylene beaker.

6.6 **Special precautions for disposal**

No special requirements.
7 MARKETING AUTHORISATION HOLDER
Aventis Pharma Limited
50 Kings Hill Avenue
Kings Hill
West Malling
Kent
ME19 4AH
UK

or trading as:-

Sanofi-aventis
One Onslow Street
Guildford
Surrey, GU1 4YS, UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 04425/0665

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION
01/02/2010

10 DATE OF REVISION OF THE TEXT
01/02/2010
PATIENT INFORMATION LEAFLET

No leaflet has been provided. In accordance with the medicines legislation, the product shall not be marketed in the UK until prior approval of the product labelling and leaflet mock-ups has been obtained.
LABELLING

No labels have been provided. In accordance with the medicines legislation, the product shall not be marketed in the UK until prior approval of the product labelling and leaflet mock-ups has been obtained.