RESTRICTED COMMERCIAL **SCOP/95/9TH MEETING**
CPS/CSM 95/10TH MEETING

NOT FOR PUBLICATION

COMMITTEE ON SAFETY OF MEDICINES

SUB-COMMITTEE ON PHARMACOVIGILANCE

SUB-COMMITTEE ON CHEMISTRY, PHARMACY AND STANDARDS

Title of Paper:
Variation Application to Request a.Change in Legal Status for Carbocisteine as an expectorant
Type of Paper: UK POM to P request.

Product: [redacted]	**Assessors:** [redacted]
Active Constituents: Carbocisteine	**Previous assessments:** None
Therapeutic classification: Mucolytic	
Legal Status: Pharmacy status requested	
Company name: [redacted]	
Sale and Supply: From registered pharmacies only	

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1. INTRODUCTION

This is an application to change the legal status of carbocisteine to permit Pharmacy sale for 3 products, [redacted], [redacted] and [redacted]. (Annex I) The currently licensed indications for the products as Prescription only medicines are:-

> [redacted] *agent for the **adjunctive therapy** of respiratory tract disorders characterised by excessive or viscous sputum."*
>
> (Further qualified for [redacted] and [redacted] - ... *"including suppurative otitis media (glue ear) and chronic obstructive airway disease"*)

The company wish to make the products additionally available for Pharmacy sale with the licensed indications:-

> "[redacted] *reduces the viscosity of mucus, helping expectoration. Recommended for the **treatment** of conditions of the respiratory tract (chest, throat, airways) where loosening of mucus is required such as in **chesty coughs** including those associated with bronchitic conditions."*
>
> (Bronchitic conditions not included for [redacted].)

No change is requested in the licensed dose i.e.

Adults -	Initially 2250 mg daily Maintenance 1500mg daily
Children -	20mg/kg/day.

The applications are supported by a review of the efficacy and safety data available, which is however largely restricted to adjunctive therapy in the treatment of chronic bronchitis/chronic obstructive airways disease.

2. BACKGROUND

Carbocisteine is currently included on the POM order. Although available for use since 1956, it was first licensed in the UK in 1972 as [redacted]). This is the first application to request a change in the legal status for carbocisteine from Prescription Only Medicine to a Pharmacy Medicine. Other mucolytic agents such as acetylcysteine are also currently POM. Other expectorants such as guiaphenesin, which has a different mode of action from carbocisteine, are GSL. Carbocisteine is available as an "over-the-counter" medicine in other EEC member states, including Ireland, Germany and the Netherlands.

3. PHARMACEUTICAL ASSESSMENT

The applications are variations to granted licences and there are no quality issues of concern.

Label and Leaflets

The proposed labels and leaflets are satisfactory, subject to approval of the Pharmacy availability and resolution of the following queries:

3.1 **Product Names** - Suitable names should be proposed to differentiate between the P and POM products.

3.2. **Labels** - Where appropriate, these should state the sodium content; that the product contains lactose ( ); and in the case of the parahydroxybenzoic acid (salts and esters) and sucrose.

4. MEDICAL ASSESSMENT

4.1 Medical Background

"Mucolytics are often presented to facilitate expectoration by reducing sputum viscosity in chronic asthma and bronchitis. Few patients, however, have been shown to derive much benefit from them although they do render sputum less viscid" (BNF Number 30, September 1995 - Annex 2(a)).

"Various compounds have been reported to act as expectorants, but there is little incidence that any of them is of any practical value... Mucolytic expectorants supposedly act by decreasing sputum viscosity. Although they can certainly be shown to have that effect (*in-vitro*), their efficacy is unproven, and they are probably no better then inhalations of steam or menthol." (pg.302 - Annex 2(b)).

, further comments. "The place of carbocisteine in clinical practice has not been firmly established and the case for its use is "not proven". This is reflected in its no longer being available on a British National Health Service prescription - except for patients under the age of 18 years who have airways disease or damage which has required tracheotomy.". (Annex 2(c)).

The assessors' therefore conclude that the therapeutic utility of mucolytics in general, and of carbocisteine specifically, remains ill defined.

4.2 Pharmacology

Acetylcysteine decreases the viscosity of sputum by splitting the disulphide bonds of glycoprotein chains. Carbocisteine is a derivative in which the disulphide group is blocked by a carboxylic acid residue. It may be only partly, if at all, directly mucolytic, and its major action is thought to be on the metabolism of

mucus-producing cells. The mucus produced has an increased sialomucin content and a reduced fucomucin content. Sialomucins influence the rheological properties of mucus and may also, through inhibition of kinins, reduce or prevent bronchial inflammation and bronchospasm.

4.3 Pharmacokinetics

Carbocisteine is promptly absorbed after oral administration and the kinetics fit a one-compartment open model. Peak concentration is reached at 1.09 hours for syrup preparations and 1.70 hours for capsules. The plasma half-life is estimated at 1.33 hours and the apparent volume of distribution is 60.4 hours.

4.4 Efficacy

4.4.1 Clinical Pharmacology Studies

Four clinical pharmacology studies are cited by the Clinical Expert in support of the effect of carbocisteine treatment on mucociliary clearance in the proposed non-prescription indication, although all were conducted in patients with chronic lung disease. (Table I, pg 10, Clinical Expert Report - Annex III).

Two of the studies failed to show a treatment effect. Only the Todisco study in COAD (n=10, 6 with Ca bronchus) demonstrated significantly improved mucociliary clearance, but at a dose considerably in excess of the initial licensed dose of 2.25gms, when administered for 15 days. Stratification of the Kohler study (n=18) demonstrated improved clearance in the sub-group with poor clearance at baseline. (The daily dose was low (1.125g) however.)

The assessors note that no consistent effect was demonstrable at 7 days or less (the potential target population for the proposed 'chesty cough indication'), the verification of low initial mucociliary clearance would require hospital diagnosis, and no studies have been conducted in patients with acute respiratory illness relevant to the proposed Pharmacy indications.

4.4.2 Clinical Studies in Adults

The applicant has identified and summarised 29 controlled clinical studies among their unpublished studies and from the published literature (including the 4 clinical pharmacology studies above), involving 1214 patients, 656 of whom received carbocisteine treatment. The clinical expert refers to the fact that 28 of these studies demonstrated a beneficial effect in some or all of the parameters evaluated, and is consistent with efficacy in the currently licensed indications. (Annex III, pg11).

The clinical expert argues that "the beneficial effects of carbocisteine in relieving the symptoms of productive cough are useful whether the cause of the cough is

chronic bronchitis or a more acute condition such as the common cold (Annex III pg. 9). This extrapolation may well not be justifiable, and the reference to the common cold may in particular be inappropriate and suggests a potential for misuse if the indication requested was approved.

The clinical expert further identifies and lists in Table II, 10 of those studies as being "the best reported of the double blind studies" and the assessors therefore conclude that the remainder provide little data of adequate standard.

All the "best reported studies" included only patients with chronic obstructive airways disease, bronchiectasis or chronic asthma. They are of limited relevance to the requested indication. The assessors' further note that differential clinical benefit was supported by objective lung function tests in only 3 studies.

4.4.3 Clinical Studies in Children

The clinical expert states that efficacy in children with respiratory disease has been less extensively studied than in adults. Eight trials were identified involving 389 children in total (Table III pg. 15/16- Annex III). Only one study was a randomised double-blind controlled study (vs. placebo) and this utilised a 30mg/kg dosage regimen, which is considerably in excess of the licensed dose of 20mg/kg. Nevertheless 'ease of expectoration' and 'overall clinical evaluation' were superior to placebo.

Only 'supportive' evidence of efficacy in children is available.

4.5 **Safety**

4.5.1 Clinical Trials in Adults

Documented adverse event data are available from 22 studies involving 548 patients who received carbocisteine and 323 patients who received placebo, and are summarised in Table IV, pg. 18 - Annex III. It should be noted that the age range is quoted as 40 to 80 years (no mean) and treatment duration varied from 4 days to 6 months.

The incidence of adverse events reported was lower on carbocisteine (6.4%) than that on placebo (9.3%) and in both groups were most frequently minor gastrointestinal disturbances. Attribution was confounded by concomitant therapy with antibiotics or cortico-steroids.

There were few serious adverse events (atrial fibrillation and acute heart failure in 2 carbocisteine patients, and status asthmaticus in one placebo patient) and were considered not unexpected in the age group and with the disease history of the patients being treated. Only occasional minor and clinically insignificant laboratory abnormalities were reported, and where recorded there were no effects on ECG, blood pressure or heart rate.

An additional large open general practice study in Germany, involving 340 patients, of whom interestingly 14 received carbocisteine 2.25g daily as **monotherapy** for up to 14 or 21 days. Side-effects were reported in 20 patients (5.9%), again most commonly gastralgia, only 3 of whom received carbocisteine alone (Table VII, pg. 20 - Annex III).

4.5.2 Clinical Studies in Children

There were only 4 isolated reports of minor adverse events from an exposed population of 272 patients, 126 (44%) of whom were 5 years old or less. (TableVIII, pg. 21 - Annex III)

4.5.3 Spontaneous Reports of Suspected Adverse Reactions

There are 119 reports of 153 suspected adverse reactions on the ADROIT database up to 6 October 1995, and no new ADR's have been reported since tabulation and review of the reports by the Clinical Expert in April of this year. (Table IX, pg. 22, Annex III, UK DAP 6.10.95 - Annex IV).

Skin and sub-cutaneous tissue disorders were most frequently reported (42%), most commonly rashes (31) or urticaria/angioedema (18). Gastrointestinal disorders account for 15% of reactions, including 4 cases of bleeding. Concomitant medication, particularly antibiotics, was frequent. None of the reactions were fatal.

Three potential interactions were reported: [redacted] reported increased somnolence when carbocisteine was prescribed for 3 days for a 64 year old receiving phenobarbitone: [redacted] reported hallucinations occurring for one day in a 67 year female receiving acyclovir, folic acid, aludrox, naproxen, alfacalcidol and buprenorphine: [redacted] describes a 9 year old who suffered a recurrence of convulsions previously well controlled on carbamazepine for six weeks and in whom a positive rechallenge was demonstrated.

The Company estimate that 2.9 million prescriptions for [redacted] have been written since 1980. The reporting rate for all carbocisteine products is therefore not more than 0.003% overall, and 0.0001% for serious gastrointestinal events. The Company also note however that the overall reporting rate for children was somewhat higher (0.01%).

There is one foreign suspected ADR report on the ADROIT database ([redacted]). This is a complex and confounded case report from Japan, occurring in an 18 year old male who was treated with cefadronil, cefpodoxime, naproxen, mequitazine and carbocisteine for a respiratory tract infection and developed Stevens-Johnson syndrome, disseminated intravascular coagulation and fatal multiple organ failure. The Company briefly refer to 2 further reports from Germany, including one of gastrointestinal symptoms and one of dyspnoea.

The assessors note that the Spontaneous Reporting Rate is low, and that no serious and unexpected adverse reactions have been reported. Gastric upset appears to be the most consistently reported adverse effect. No safety concerns emerge from these data.

4.5.4 Safety in Overdose

The clinical expert reports that the Medical Toxicology Unit of Guy's and St Thomas' Hospital Trust indicates that [redacted] was involved in 46 cases of overdose, 38 of which were asymptomatic. Symptoms reported included vomiting, abdominal pain, hysteria/aggression following ingestion of 20 capsules, drowsiness which in one case followed ingestion of 100ml syrup, and tachycardia. The Medical Toxicology Unit concluded that carbocisteine has a low order of toxicity in acute overdosage.

4.5.5 Other Safety Considerations

There are no known clinically important drug interactions with [redacted] One safety study was however conducted by Domshke et al (Acta Hepato-Gastroenterol 1976; 23: 213-5) in 10 healthy male volunteers to assess the effect of the licensed dose of [redacted] on gastric secretions. No differences were detected during either basal gastric secretion or pentagastrin-stimulated secretion.

4.6 **Basis for Legal Classification - Assessors Comments**

The criteria for classifying medicinal products as Prescription-only Medicines and an Aide-memoir on making POM to P switches are appended as Annexes Va and Vb.

The assessors conclude that the indications for use of [redacted] should remain restricted to the currently licensed indications for use as adjunctive therapy in the absence of any substantive data for efficacy in the treatment of "chesty coughs".

The therapeutic utility of mucolytics in general, and specifically carbocisteine remains ill defined despite investigation and use over many years in the licensed indications. Usage in children may be predominantly for chronic respiratory conditions such as cystic fibrosis or bronchiectasis. Efficacy has not been demonstrated in "chesty coughs" either in adults or children. It therefore appears that [redacted] products *"contain substances or preparations thereof the activity and/or side effects of which require further investigation".*

It is submitted that [redacted] is unsuitable for self medication and self-diagnosis. The data available clearly indicate that the medical prescription of [redacted] in the adjunctive therapy of chronic obstructive airways disease (bronchietiasis/chronic asthma) is in the nature of an individual therapeutic trial and clinical responders cannot be identified with certainty before exposure. Frequent medical assessment and supervision is required on a regular basis. It therefore follows that "*they are likely to present a direct or indirect danger to*

human health, even when used correctly, if used without the supervison of a doctor (or dentist)".

Furthermore, were the requested indications for a Pharmacy product agreed, use in children or adults for "chesty coughs" might well delay medical advice for potentially life threatening respiratory tract infections. [redacted] products could therefore be *"frequently and to a very wide extent used incorrectly, and as a result would be likely to present a direct or indirect danger to health".*

5. ASSESSORS' CONCLUSIONS

No evidence of efficacy in the proposed indications for use as a Pharmacy product has been submitted.

The therapeutic utility of carbocisteine remains ill defined. The appropriate use of [redacted]/carbocisteine within the existing licensed indications requires careful and frequent medical assessment and supervision on a regular basis. Pharmacy legal status is therefore inappropriate.

There are no direct safety concerns.

[redacted]

[redacted]

INDEX OF ATTACHMENTS

Annex 1 Product Licence Variation - MLA 201/Labels and Leaflets

Annex II

(i) BNF No 30, Sept. 1995, pg. 142/3, Mucolytics
(ii) Expectorants, Grahame-Smith & Aranson 1992, pg. 302.
(iii) Carbocisteine, Dollery 1991, pg 71-71

Annex III Clinical Expert Report

Annex IV Carbocisteine ADROIT DAP

Annex V

(i) Criteria for Clarifying Medicinal Products as Prescription Only Medicines
(ii) Aid memoir on making POM to P Switches

Name of MA holder: [redacted] Product name: [redacted]

MA number: [redacted]

RELATED APPLICATIONS (S) *(Please specify including date of pending renewal application(s))*

BACKGROUND *(Please give brief background explanation for the proposed changes* to your MA)
APPLICATION SEEKING CHANGE IN LEGAL STATUS FROM PRESCRIPTION ONLY MEDICINE TO PHARAMCY MEDICINE

(Specify the precise present and proposed wording or specification. For SPC changes, underline or highlight the changed words and attach a complete new version)

PRESENT	PROPOSED
LEGAL STATUS PRESCRIPTION RECOMMENDED CLINICAL INDICATIONS AND ROUTE OF ADMINSTRATION MUCOLYTIC AGENT FOR THE ADJUNCTIVE THERAPY OF RESPIRATORY TRACT DISORDERS CHARACTERISED BY EXCESSIVE OR VISCOUS MUCUS.	LEGAL STATUS PHARAMCY RECOMMENDED CLINICAL INDICATIONS AND ROUTE OF ADMINSTRATION WHEN PRESCRIBED BY A DOCTOR MUCOLYTIC AGENT FOR THE ADJUNCTIVE THERAPY OF RESPIRATORY TRACT DISORDERS CHARACTERISED BY EXCESSIVE OR VISCOUS MUCUS WHEN SOLD IN A PHARAMCY WITHOUT A DOCTORS PRESCRIPTION [redacted] REDUCES THE VISCOSITY OF MUCUS, HELPING EXPECTORATION. RECOMMENDED FOR THE TREATMENT OF CONDITIONS OF THE RESPIRATORY TRACT (CHEST, THROAT, AIRWAYS) WHERE LOOSENING OF MUCUS IS REQUIRED SUCH AS IN CHESTY COUGHS.

I hereby make application for the above Marketing Authorization to be varied in accordance with the proposals given above and certify that the changes will not adversely affect the quality, efficacy or safety of the product. I declare that amended documents have been supplied and that the supporting information, where appropriate, meets the Type I conditions or supports the proposed Type II change. I declare that all changes have been identified and that there are not other changes in the amended documentation.

Fees paid. Please specify category under National/Community rules

Amount/Currency [redacted]

Main Signatory [redacted] **Status (Job title)** [redacted]

Print name [redacted] **Date** 23/6/95

Second Signatory (where appropriate **Status (Job title)**

Print name **Date**

Name of MA holder: [redacted] Product name: [redacted]

MA number: [redacted]

RELATED APPLICATIONS (S) *(Please specify including date of pending renewal application(s))*

BACKGROUND *(Please give brief background explanation for the proposed changes* to your MA)
APPLICATION SEEKING CHANGE IN LEGAL STATUS FROM PRESCRIPTION ONLY MEDICINE TO PHARAMCY MEDICINE

(Specify the precise present and proposed wording or specification. For SPC changes, underline or highlight the changed words and attach a complete new version)

PRESENT	PROPOSED
LEGAL STATUS PRESCRIPTION RECOMMENDED CLINICAL INDICATIONS AND ROUTE OF ADMINSTRATION MUCOLYTIC AGENT FOR THE ADJUNCTIVE THERAPY OF RESPIRATORY TRACT DISORDERS CHARACTERISED BY EXCESSIVE OR VISCOUS MUCUS, INCLUDING SUPPURATIVE OTITIS MEDIA (GLUE EAR) AND CHRONIC OBSTRUCTIVE AIRWAY DISEASE..	LEGAL STATUS PHARAMCY X RECOMMENDED CLINICAL INDICATIONS AND ROUTE OF ADMINSTRATION WHEN PRESCRIBED BY A DOCTOR MUCOLYTIC AGENT FOR THE ADJUNCTIVE THERAPY OF RESPIRATORY TRACT DISORDERS CHARACTERISED BY EXCESSIVE OR VISCOUS MUCUS, INCLUDING SUPPURATIVE OTITIS MEDIA (GLUE EAR) AND CHRONIC OBSTRUCTIVE AIRWAY DISEASE WHEN SOLD IN A PHARAMCY WITHOUT A DOCTORS PRESCRIPTION [redacted] REDUCES THE VISCOSITY OF MUCUS, HELPING EXPECTORATION. RECOMMENDED FOR THE TREATMENT OF CONDITIONS OF THE RESPIRATORY TRACT (CHEST, THROAT, AIRWAYS) WHERE LOOSENING OF MUCUS IS REQUIRED SUCH AS IN CHESTY COUGHS, INCLUDING THOSE ASSOCIATED WITH BRONCHITIC CONDITIONS.

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Fees paid. Please specify category under National/Community rules [redacted]

Amount/Currency

Main Signatory [redacted] Status (Job title) [redacted]

Print name [redacted] Date 26/5/95

Second Signatory (where appropriate Status (Job title)

Name of MA holder: [redacted] Product name: [redacted]

MA number: [redacted]

RELATED APPLICATIONS (S) *(Please specify including date of pending renewal application(s))*

BACKGROUND *(Please give brief background explanation for the proposed changes* to your MA)
APPLICATION SEEKING CHANGE IN LEGAL STATUS FROM PRESCRIPTION ONLY MEDICINE TO PHARAMCY MEDICINE

(Specify the precise present and proposed wording or specification. For SPC changes, underline or highlight the changed words and attach a complete new version)

PRESENT	PROPOSED
LEGAL STATUS PRESCRIPTION RECOMMENDED CLINICAL INDICATIONS AND ROUTE OF ADMINSTRATION MUCOLYTIC AGENT FOR THE ADJUNCTIVE THERAPY OF RESPIRATORY TRACT DISORDERS CHARACTERISED BY EXCESSIVE OR VISCOUS MUCUS, INCLUDING SUPPURATIVE OTITIS MEDIA (GLUE EAR) AND CHRONIC OBSTRUCTIVE AIRWAY DISEASE..	LEGAL STATUS PHARAMCY RECOMMENDED CLINICAL INDICATIONS AND ROUTE OF ADMINSTRATION WHEN PRESCRIBED BY A DOCTOR MUCOLYTIC AGENT FOR THE ADJUNCTIVE THERAPY OF RESPIRATORY TRACT DISORDERS CHARACTERISED BY EXCESSIVE OR VISCOUS MUCUS, INCLUDING SUPPURATIVE OTITIS MEDIA (GLUE EAR) AND CHRONIC OBSTRUCTIVE AIRWAY DISEASE WHEN SOLD IN A PHARAMCY WITHOUT A DOCTORS PRESCRIPTION [redacted] REDUCES THE VISCOSITY OF MUCUS, HELPING EXPECTORATION. RECOMMENDED FOR THE TREATMENT OF CONDITIONS OF THE RESPIRATORY TRACT (CHEST, THROAT, AIRWAYS) WHERE LOOSENING OF MUCUS IS REQUIRED SUCH AS IN CHESTY COUGHS, INCLUDING THOSE ASSOCIATED WITH BRONCHITIC CONDITIONS.

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Fees paid. Please specify category under National/Community rules

Amount/Currency [redacted]

Main Signator [redacted] Status (Job title) [redacted]

Print name [redacted] Date 23/6/95

Second Signatory (where appropriate) Status (Job title)

Front surface of carton/bottle label.

[redacted]

Loosens and clears difficulty chesty coughs including those associated with bronchitic conditions.

Rear surface of Carton/Capsule container.

[redacted] [redacted]
Each capsule contains 375 mg carbocisteine.

[redacted] loosen and clear difficult chesty coughs including those associated with bronchitic conditions.

When prescribed by a doctor it may be used in the treatment of glue ear.

Dose:

Adults including the elderly:
Initial Dose: Two capsules three times a day
When the chesty cough begins to improve. One capsule 4 times a day.

Children: Should use [redacted]

If symptoms do not improve you should consult your doctor.

You should not use [redacted] if you have a stomach ulcer.

If you are pregnant or breast feeding your baby you should only use [redacted] if they have been prescribed for you by your doctor. [redacted] is not recommended in the first trimester of pregnancy.

[redacted] do not normally have any effects on the ability to drive or operate machinery.

Keep all medicines out of the reach of children.

[redacted] Legal Status P

[redacted]

Lot no. Expiry date

[redacted]

Front surface of carton/bottle label.

[redacted]

Loosens and clears difficult chesty coughs including those associated with bronchitic conditions.

Rear surface of carton/bottle label.

[redacted] [redacted]
Each 5 ml contains 250 mg carbocisteine.

[redacted] loosens and clears difficult chesty coughs including those associated with bronchitic conditions.

When prescribed by a doctor it may be used in the treatment of glue ear.

Dose:
Adults including the elderly:
Initial Dose: Three 5 ml spoonfuls three times a day
When an improvement is noticed dose should be reduced to: Two 5 ml spoonfuls three times a day.

Children: Should use [redacted]
If symptoms do not improve you should consult your doctor.

You should not use [redacted] if you have a stomach ulcer.

If you are pregnant or breast feeding your baby you should only use [redacted] if it has been prescribed for you by your doctor. [redacted] is not recommended in the first trimester of pregnancy.

You should not take [redacted] at the same time a Pholcodine Linctus (a medicine for suppressing coughs) and neither should [redacted] be mixed with Pholcodine Linctus.

[redacted] does not normally have any effects on the ability to drive or operate machinery.

Keep all medicines out of the reach of children.

Store below 25°C.

[redacted] Legal Status P

[redacted]

Lot No. Expiry Date:

Carton & Label Text for [redacted]

Front surface of carton/bottle label.

[redacted]

Loosens and clears difficult chesty coughs.

Rear surface of carton/bottle label.

[redacted] [redacted]

Each 5 ml contains 125 mg carbocisteine.

[redacted] loosens and clears difficult chesty coughs.

Dose:

Children aged 5-12 years	Two 5 ml spoonfuls three times a day.
2-5 years	Half to one 5 ml spoonful four times a day.

If symptoms do not improve medical attention should be obtained.

You should not give [redacted] if your child has stomach troubles.

[redacted] should not be used by anyone who is pregnant or breast feeding a baby unless it has been prescribed by a doctor. It is not recommended in the first trimester of pregnancy.

Does not normally cause any drowsiness

Keep all medicines out of the reach of children.

Store in a cool place.

[redacted] Legal Status P

[redacted]

Lot No. Expiry Date:

Patient Information Leaflet

[redacted]

Each capsule contains 375 mg carbocisteine. It also contains magnesium stearate, Aerosil (colloidal silicon dioxide), lactose, sodium lauryl sulphate. The gelatin capsule contains E102.

This pack contains 30 capsules.

[redacted] is a medicine which reduces the viscosity (loosens) mucus particularly in chesty coughs thereby easing and soothing.

[redacted] is manufactured by [redacted]

What is [redacted] for?

[redacted] is recommended for difficult chesty coughs including those associated with bronchitic conditions where it loosens and clears difficult mucus.

When prescribed by a doctor [redacted] can be used in the treatment of glue ear.

When should you not use [redacted]

You should not use [redacted] if you have a stomach ulcer.

You should not take [redacted] if you are pregnant or breast feeding your baby unless it has been prescribed for you by you doctor. [redacted] is not recommended in the first three months of pregnancy.

[redacted] does not normally have any effects on the ability to drive or operate machinery.

What is the dose of [redacted]?

Adults (including the elderly).

Initial Dose:	Two capsules three times a day
When the chesty cough begins to improve reduce dosage to:	One capsule four times a day

Children: Should use [redacted]
If symptoms do not improve you should consult your doctor.

If more than the recommended amount of [redacted] are taken you should seek advice from your doctor or nearest hospital casualty department.

Can unwanted effects occur after using [redacted] Capsules?

Rarely there have been reports of skin rashes and gastro-intestinal disturbances following treatment with [redacted]
If you notice anything unusual you should ask your doctor.

[redacted] should not be taken if the capsules have passed the expiry date in the label.

Keep all medicines out of the reach of children

Date of preparation: June 1995

If you would like more information about the medicine we recommend that you ask your Pharmacist.

Patient Information Leaflet

[redacted]

Each 5 ml spoonful of [redacted] contains 250 mg carbocisteine.

It also contains Nipagin in Sodium, sucrose, caramel liquid, rum and cinnamon flavours sodium hydroxide, hydrochloric acid and water.

This pack contains 200 ml [redacted].

[redacted] is a medicine which reduces the viscosity (loosens) mucus particularly in chesty coughs thereby easing and soothing.

[redacted] is manufactured by [redacted]

What is [redacted] for?

[redacted] is recommended for the treatment of chesty coughs including those associated with bronchitic conditions where it loosens and clears difficult mucus.

When prescribed by a doctor [redacted] may be used in the treatment of glue ear.

When should you not use [redacted]?

You should not use [redacted] if you have a stomach ulcer.

You should not take [redacted] if you are pregnant or breast feeding your baby unless it has prescribed for you by your doctor. [redacted] is not recommended in the first three months of pregnancy.

You should not take [redacted] at the same time as Pholcodine Linctus (a medicine for suppressing coughs) and neither should you mix Pholcodine Linctus with [redacted]

[redacted] does not normally have any effects on the ability to drive or operate machinery.

What is the dose of [redacted]?

Adults (including the elderly)
Initial Day: Three 5 ml spoonfuls three times a day.
When an improvement is
noticed dose should be reduced to: Two 5 ml spoonfuls three times a day.

Children: should use [redacted]
If symptoms do not improve you should consult your doctor.
If more than the recommended amount of [redacted] is taken you should seek advice from your doctor or nearest hospital casualty department.

Can unwanted effects occur after using [redacted]?

Rarely there have been reports of skin rashes and gastro-intestinal disturbances following treatment with [redacted] If you notice anything unusual you should consult your doctor.

[redacted] should not be taken if the syrup has passed the expiry date on the label.

[redacted] should be stored below 25°C.

Keep all medicines out of the reach of children.

Date of Preparation June 1995

If you would like more information about this medicine we recommend that you ask your Pharmacist.

Patient Information Leaflet

[redacted]

Each 5 ml spoonful of [redacted] contains 125 mg carbocisteine.

It also contains sucrose, sodium methyl hydroxybenzoate, vanillin, raspberry and cherry flavours, colouring (E 124) sodium hydroxide solution, hydrochloric acid and water.

This pack contains 200 ml [redacted].

[redacted] is a medicine which reduces the viscosity (loosens) mucus particularly in chesty coughs thereby easing and soothing.

[redacted] is manufactured by [redacted]

What is [redacted] for?

[redacted] is recommended for chesty coughs where it loosens and clears difficult mucus.

When should you not give [redacted]

You should not give [redacted] to a child who has stomach troubles.

[redacted] should not be given to anyone who is pregnant or breast feeding unless it has been prescribed by a doctor, [redacted] is not recommended in the first three months of pregnancy.

What is the dose of [redacted]

Children 5-12 years	Two 5 ml spoonfuls three times a day
Children 2-5 years	Half to one 5 ml spoonful four times a day.

If symptoms do not improve your child should see their doctor.

If more than the recommended amount of [redacted] is taken you should seek advice from your doctor or nearest hospital casualty department.

Can unwanted effects occur after using [redacted]

Carbocisteine, the active ingredient of [redacted] has rarely been associated with skin rashes and gastro-intestinal disturbances.
If your child experiences anything unusual you should consult their doctor.

[redacted] does not normally cause any drowsiness.

[redacted] should not be taken if the syrup has passed the expiry date on the label.

The syrup should be stored in a cool place.

If your pharmacist needs to dilute this product for you, this should be carried out with Unpreserved Syrup B.P. and the diluted preparation should not be used beyond 14 days after dilution.

Keep all medicines out of the reach of children.

Date of preparation: June 1995

If you would like more information about this medicine you should consult your Doctor or Pharmacist.

lists of pharmacy contractors who provide domiciliary oxygen services.

Patients are supplied with either constant or variable performance masks. The Intersurgical 010 28% or Ventimask MK IV 28% are constant performance masks and provide a nearly constant supply of oxygen (28%) over a wide range irrespective of the patient's breathing pattern. The variable performance masks include the Intersurgical 005 Mask and the Venticare Mask, the concentration of oxygen supplied to the patient varies with the rate of flow of oxygen and also with the patient's breathing pattern.

OXYGEN CONCENTRATORS

Long-term administration of oxygen (at least 15 hours daily) may prolong survival in patients with severe chronic obstructive airways disease with cor pulmonale.

Department of Health guidelines suggest that this treatment should be provided for patients who fulfil the following criteria

$P_aO_2 < 7.3$kPa, $P_aCO_2 > 6$kPa.

$FEV_1 < 1.5$ litre and $FVC < 2$ litre

The measurements should be stable on two occasions at least three weeks apart after the patient has received appropriate bronchodilator therapy.

Less information is available on long-term oxygen in patients with a similar degree of hypoxaemia and airflow obstruction *but no hypercapnia*; the Department of Health suggests that these patients should not be denied this form of treatment but the effects of long term therapy have not yet been assessed completely.

Increased respiratory depression from low concentrations of oxygen is seldom a problem in patients with stable respiratory failure although it may occur during exacerbations; patients and relatives should be warned to call for medical help if drowsiness or confusion occur.

Oxygen concentrators are more economical for patients requiring oxygen for long periods, and in England and Wales are now prescribable on the NHS on a regional tendering basis (see below). A concentrator was formerly only provided for a patient who required oxygen for 15 hours a day but it has been found to be cost-effective to provide one for a patient requiring it for 8 hours a day (or 21 cylinders per month).

PRESCRIBING ARRANGEMENTS FOR OXYGEN CONCENTRATORS

Prescribe concentrator and accessories (face mask, nasal cannula, and humidifier) on form FP10. Specify amount of oxygen required (hours per day) and flow rate. If required, prescribe back-up oxygen set and cylinder at same time. Inform patient that the supplier will be in contact to make arrangements and that the prescription form is to be given to the person who installs the concentrator.

Inform supplier by telephone (see table below) that a concentrator has been prescribed. The supplier will send written confirmation of the order to the prescriber, the patient, and the FHSA.

Follow the same procedure if a back-up oxygen set and cylinder are required later.

FHSA regional group	Supplier
Eastern North Western London North North Wales West Midlands	De Vilbiss Health Care Ltd *to order* Dial 0800 020202
London South (includes Kent, Surrey, and Sussex)	Omnicare Group Ltd *to order* Dial 100 *and ask for* Freephone Omnicare Oxygen
Central and South Wales Northern South Western Yorkshire (South and West) and Humberside	Oxygen Therapy Co Ltd *to order* Dial 0800 373580

In Scotland refer the patient for assessment by a respiratory consultant. If the need for a concentrator is confirmed the consultant will arrange for the provision of a concentrator through the Common Services Agency.

3.7 Mucolytics

Mucolytics are often prescribed to facilitate expectoration by reducing sputum viscosity in chronic asthma and bronchitis. Few patients, however, have been shown to derive much benefit from them although they do render sputum less viscid. Steam inhalation with postural drainage, is good expectorant therapy in bronchiectasis and some chronic bronchitics.

For reference to the newly introduced dornase alfa, see below.

ACETYLCYSTEINE

Indications: reduction of sputum viscosity

Side-effects: occasional gastro-intestinal irritation, headache, urticaria, tinnitus, and sensitivity

Dose: adults and children over 6 years, 200 mg in water 3 times daily, usually for 5–10 days but if necessary may be extended to 6 months or longer; CHILD up to 2 years 200 mg daily, 2–6 years 200 mg twice daily

NHS * PoM Acetylcysteine Granules (Non-proprietary)

Granules, acetylcysteine 200 mg/sachet. Net price 30 sachets = £5.60. Label: 13

* except for abdominal complications associated with cystic fibrosis and endorsed 'SLS' ('S2B' in Scotland)

Note. The brand name **NHS** Fabrol® (Zyma) is used for acetylcysteine granules

CARBOCISTEINE

Indications: reduction of sputum viscosity

Side-effects: occasional gastro-intestinal irritation, rashes

Dose: 750 mg 3 times daily initially, then 1.5 g daily in divided doses; CHILD 2–5 years 62.5–125 mg 4 times daily, 6–12 years 250 mg 3 times daily

NHS * PoM Carbocisteine Capsules (Non-proprietary)

Capsules, carbocisteine 375 mg. Net price 30-cap pack = £3.35

NHS * PoM Carbocisteine Syrup (Non-proprietary)

Oral liquid, carbocisteine 125 mg/5 mL, net price 300 mL = £3.68; 250 mg/5 mL, 300 mL = £4.72

* except for patients under the age of 18 years, any condition which, through damage or disease, affects the airways and has required a tracheostomy and endorsed 'SLS' ('S2B' in Scotland)

Note. The brand name **NHS** Mucodyne® (Rhône-Poulenc Rorer) *is used for carbocisteine preparations*; capsules and 250 mg/5 mL strength of syrup contain tartrazine

METHYL CYSTEINE HYDROCHLORIDE

(Mecysteine Hydrochloride)

Indications: reduction of sputum viscosity

Dose: 100–200 mg 3–4 times daily before meals reduced to 200 mg twice daily after 6 weeks; CHILD over 5 years 100 mg 3 times daily

Prophylaxis, 100–200 mg 2–3 times every other day during winter months

NHS Visclair® (Sinclair)

Tablets, yellow, s/c, e/c, methyl cysteine hydrochloride 100 mg. Net price 20 = £3.66. Label: 5, 22, 25

DORNASE ALFA

Dornase alfa is a genetically engineered version of a naturally occurring human enzyme which cleaves extracellular deoxyribonucleic acid (DNA). It is administered by inhalation using a jet nebuliser (see section 3.1.5).

DORNASE ALFA

Phosphorylated glycosylated recombinant human deoxyribonuclease 1 (rhDNase)

Indications: management of cystic fibrosis patients *with a forced vital capacity (FVC) of greater than 40% of predicted* to improve pulmonary function

Cautions: pregnancy and breast-feeding (manufacturers do not recommend)

Side-effects: pharyngitis, voice changes, laryngitis, rashes, *urticaria*

Dose: *by inhalation of nebulised solution* (by jet nebuliser), 2500 units (2.5 mg) once daily (patients over 21 years may benefit from twice daily dosage); CHILD under 5 years not recommended

▼ PoM Pulmozyme® (Roche)

Nebuliser solution, dornase alfa 1000 units (1 mg)/mL. Net price 2.5 mL (2500 units) vial = £20.[illegible]

Note. For use undiluted with jet nebulisers only; ultrasonic nebulisers are unsuitable

3.8 Aromatic inhalations

Inhalations containing volatile substances such as eucalyptus oil are traditionally used and although the vapour may contain little of the additive it encourages deliberate inspiration of warm moist air which is often comforting in bronchitis. Boiling water should not be used owing to the risk of scalding. Inhalations are also used for the relief of nasal obstruction in acute rhinitis or sinusitis.

CHILDREN. The use of strong aromatic decongestants (applied as rubs or to pillows) is not advised for infants under the age of 3 months. Mothers with young infants in whom nasal obstruction with mucus is a problem can readily be taught appropriate techniques of suction aspiration.

Benzoin Tincture, Compound, BP

(Friars' Balsam)

Tincture, balsamic acids approx. 4.5%. Label: 15

Directions for use: add one teaspoonful to a pint of hot, not boiling, water and inhale the vapour

Menthol and Eucalyptus Inhalation, BP 1980

Inhalation, racementhol or levomenthol 2 g, eucalyptus oil 10 mL, light magnesium carbonate 7 g, water to 100 mL.

Directions for use: add one teaspoonful to a pint of hot, not boiling, water and inhale the vapour

NHS Karvol® (Crookes)

Inhalation capsules, menthol 35.55 mg, with chlorbutol, pine oils, terpineol, and thymol. Net price 10 = 91p

Directions for use: inhale vapour from contents of 1 capsule expressed into handkerchief or a pint of hot, not boiling, water; avoid in infants under 3 months

3.9 Cough preparations

3.9.1 Cough suppressants

3.9.2 Expectorant and demulcent cough preparations

3.9.1 Cough suppressants

The drawbacks of prescribing cough suppressants are rarely outweighed by the benefits of treatment and only occasionally are they useful, as, for example, if sleep is disturbed by a dry cough. Cough suppressants may cause sputum retention and this may be harmful in patients with chronic bronchitis and bronchiectasis.

Opioid cough suppressants such as codeine, dextromethorphan, and pholcodine are seldom sufficiently potent to be effective in severe cough, all tend to cause constipation.

Sedative antihistamines, such as diphenhydramine, are used as the cough suppressant component of many compound cough preparations on sale to the public; all tend to cause drowsiness which may reflect their main mode of action.

ANNEX II (i)

Oxygen is not without adverse effects. The risk of worsening hypercapnia is mentioned above. Prolonged inhalation of high concentrations of inspired oxygen may have adverse effects in both neonates and adults. In neonates it can cause retrolental fibroplasia and consequent blindness. In adults it may cause irritation of the respiratory tract, with coughing, sore throat, tracheobronchitis, pulmonary oedema, and atelectasis.

24.2 Cough

If a cough is irritating and unproductive of sputum it may be suppressed. If it is associated with production of sputum, but difficulty in expectoration, then some would use expectorant drugs. These measures are used only for the symptomatic treatment of cough, and where possible the underlying condition should also be treated.

24.2.1 Cough suppressants

Opiates act as cough suppressants by a direct effect on the medullary mechanisms subserving cough. Codeine phosphate and pholcodine can be used when a dry cough is disturbing sleep, but rarely otherwise. They may cause sputum retention, and should therefore be used with caution in chronic bronchitis or bronchiectasis. The potent opiates, such as morphine and diamorphine, may sometimes be useful in the treatment of intractable dry cough in patients with terminal illness, particularly bronchogenic carcinoma.

In addition to drugs which suppress cough directly, symptomatic relief may sometimes be obtained from a simple linctus, which feels soothing to the throat.

24.2.2 Expectorants

Various compounds have been purported to act as expectorants, but there is little evidence that any of them is of any practical value. The inhalation of steam, with or without a volatile inhalant, such as menthol or benzoin, is soothing in bronchitis and bronchiectasis, and is harmless. It may be used as an adjunct to physiotherapy to aid expectoration of viscid sputum.

Mucolytic expectorants supposedly act by decreasing sputum viscosity. Although they can certainly be shown to have that effect *in vitro*, their clinical efficacy is unproven, and they are probably no better than inhalations of steam or menthol. There is a wide variety of other expectorants available, containing drugs which supposedly increase watery bronchial secretions, but which probably act as expectorants only if they cause vomiting (for example squill, ipecacuanha, ammonium chloride). There is no evidence that any of these is of any value and they are certainly toxic.

Recently, nebulized hypertonic saline (3 mL of a 6 per cent solution) and nebulized amiloride (3 mL of a 10^{-3} molar solution) have been used as expectorants in patients with bronchiectasis and cystic fibrosis, but although they may increase the volume and water content (i.e. reduce the viscosity) of the sputum, their clinical benefit is not clear.

24.3 Pneumonias

A list of infective causes of pneumonia is given in Table 24.2, along with the first-line and alternative antibiotics indicated in such cases.

The principles of treatment of infections are outlined in Chapter 22, but the following points are worth emphasizing in regard to pneumonia.

24.3.1 Drug therapy besides antibiotics

Oxygen should be given for hypoxia. If there is severe hypoxia (P_AO_2 less than 6.5 kPa) or worsening hypercapnia, ventilation may be required. Fluids should be given if there is dehydration. Mild pleuritic pain can be relieved by analgesics such as aspirin and paracetamol, or by non-steroidal anti-inflammatory drugs such as naproxen and indomethacin. More severe pain may be treated with more potent analgesics, such as buprenorphine, morphine, or pethidine, but care must be taken in patients with hypercapnia,

Carbocisteine

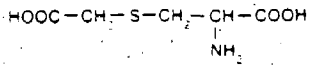
Carbocisteine was first produced in the 1930s during research into the protective nature of glutathione and cysteine against the toxicity of iodoacetate. Currently, it is used as a mucolytic agent in the adjunctive therapy of respiratory tract disorders characterized by excessive, viscous mucus.

Chemistry

Carbocisteine (carbocysteine, S-carboxymethylcysteine, Mucodyne, Mucolex)

$C_5H_9NO_4S$

S-(Carboxymethyl)-L-cysteine or 3-[(carboxymethyl)thio] alanine



Molecular weight	179.2
pKa	—
Solubility	
in alcohol	—
in water	—
Octanol/water partition coefficient	—

Carbocisteine is a white powder with no characteristic odour.

Pharmacology

The precise mechanism of action of carbocisteine is unknown. Systems in which it is pharmacologically active are described in the section on clinical pharmacology.

Toxicology

Tests in mammalian species have revealed no significant toxicity. No mutagenic, carcinogenic or teratogenic effects have been reported.

Clinical pharmacology

Acetylcysteine decreases the viscosity of sputum by splitting the disulphide bonds of glycoprotein chains. Carbocisteine is a derivative in which the sulphydryl group is blocked by a carboxylic acid residue. It may be only partly, if at all, directly mucolytic. Its major action is thought to be on the metabolism of mucus-producing cells.[1] The mucus produced under the influence of carbocisteine has an increased sialomucin content and a reduced fucomucin content. Sialomucins influence the rheological properties of mucus and may also, through inhibition of kinins, reduce or prevent bronchial inflammation and bronchospasm. This subject has been recently reviewed by Medici and Radielovic.[2] In chronic bronchitis, carbocisteine has been found by some workers to reduce sputum viscosity,[3] and by others to increase viscosity.[4] A recent study[5] examined sputum viscosity and elasticity, the latter judged by some to be the more important factor; while most patients showed reduction in both when treated with carbocisteine, two cases showed decreased viscosity with increased elasticity and one showed an increase in both. Another large study[6] showed a trend towards increase in both viscosity and elasticity but with extremely wide variation between patients. It has been suggested[4] that stable, predictable effects on sputum are not seen until after at least seven, possibly fourteen, days of treatment.

Carbocisteine has been shown to increase the forced expiratory volume in one second[3] but another study showed no such effect.[4]

Carbocisteine has been demonstrated [illegible] clearance of lung of tracheal secretions.

Studies of the use of carbocisteine in patients with otitis media with effusion have variously reported benefit[7] and no benefit.[8] It has been observed that carbocisteine does not influence the viscosity of established effusion but, given preoperatively and postoperatively, favourably influences the outcome after surgical removal of the effusion; this is said to reflect the influence of carbocisteine on mucus-producing cells.[9]

Pharmacokinetics

Published studies have employed a variety of methods for determining carbocisteine in biological fluids. These have included separation of the intact compound using an amino acid analyser, gas-liquid chromatography (GLC) using trifluoroacetic anhydride derivatization with flame-ionization detection, and GLC with a flame photometric detector in the sulphur mode.[13–15]

Carbocisteine is promptly absorbed after oral administration and the kinetics fit a one-compartment open model. Peak concentration is reached at 1.09 hours for syrup preparations and 1.70 hours for capsules; peak concentrations after a 1.5 g dose are 13.38 and 12.40 mg.l^{-1} respectively. The plasma half life is estimated at 1.3 hours. The apparent volume of distribution is 60.4 l.[15] There is no information on intravenous studies to allow bioavailability determination. There is no reported work on first-pass metabolism or protein binding.

Studies using the lysine salt of carbocisteine have shown that up to 17.5% of an oral dose penetrates bronchial mucus. Peak concentration in mucus is at 2.0 hours and half life is 1.82 hours.[14] In mice and guinea-pigs, the highest concentration of carbocisteine (after oral administration) occurs in liver, kidney, pancreas, spleen and lung. Very little is found in brain. Levels are best maintained in lung tissue.[16]

Oral absorption	extensive
Presystemic metabolism	—
Plasma half life	
mean	1.33 h
Volume of distribution	60.4 l
Plasma protein binding	—

Concentration–effect relationship

There are no data to suggest a relevant relationship between concentration and effect.

Metabolism

Using ^{35}S-labelled carbocisteine it has been observed that only 0.3% appears in faeces over a three-day period after a single oral dose. A the rest is excreted in the urine.[17] Much of it is excreted unchanged but with wide individual variation (range 29–83%).[18] There similar, wide variation in the pattern of metabolism, the maj pathways in man being acetylation, decarboxylation and sulphoxidation. Two out of three individuals excrete a glucuronic acid conjuga as a minor metabolite.[19,20] There are no reports of pharmacolog cally important activity in these metabolites. There is evidence th the sulphoxidation of carbocisteine is under monogenic control.

Pharmaceutics

Carbocisteine is available in the UK in a number of oral forms:

1. Mucodyne capsules (Rorer, UK): opaque, yellow capsules marked 'Mucodyne 375' (Rorer, UK) each containing carbocisteine 375 mg. Also as Mucolex (Warner, UK) round convex orange tablets.
2. Mucodyne syrup (Rorer, UK): clear amber syrup containing 250 mg carbocisteine in 5 ml; also as Mucolex syrup (Parke-Davis, UK) with a raspberry-menthol flavour.
3. Mucodyne syrup forte: opaque, orange syrup containing 750 m carbocisteine in 5 ml.
4. Mucodyne paediatric: clear, red syrup containing 125 mg carbocisteine in 5 ml.

All preparations should be protected from light and not subjected to temperatures above 25°C. The syrups can be diluted with unpreserved syrup BP but should be kept for only 14 days thereafter. Mixture of the syrup with pholcodeine linctus causes precipitation of the carbocisteine.

Therapeutic use

Indications

The approved indication is as an adjunctive therapy for those respiratory tract disorders characterized by excessive and/or viscous mucus, including 'glue-ear' in children.

Contraindications

There are no contraindications (see Concurrent disease).

Mode of use

In adults the initial daily dose is 2250 mg in divided doses, reducing to 1500 mg when a satisfactory clinical response has been obtained. In children the normal daily dose is 20 mg kg^{-1} body weight in divided doses, given as paediatric syrup. For children aged 2–5 years, 2.5–5 ml four times a day; 5–12 years, 10 ml three times a day. There is no recommended schedule for children under 2 years. The manufacturers do not suggest how long treatment should be continued, though it may take at least seven days before an effect is seen.[4]

Indications

The place of carbocisteine in clinical practice has not been firmly established and the case for its use is 'not proven'. This is reflected in its no longer being available on a British National Health Service prescription — except for patients under the age of 18 years who have airways disease or damage which has required tracheostomy.

Adverse reactions

Potentially life-threatening effects
There are no reports of such effects with carbocisteine and no reports of death associated with its use.

Acute overdosage
Gastrointestinal disturbance is the only likely symptom and no active treatment is necessary.

Severe or irreversible adverse effects
The very few suspected reactions associated with carbocisteine therapy reported to the Committee on Safety of Medicines include gastrointestinal bleeding and convulsions, but a causal relationship has not been established.

Symptomatic adverse effects
These are very rare (only 22 reports to the Committee on Safety of Medicines between 1964 and 1984). Reported reactions are skin rashes, nausea, headaches, myalgia, dizziness, urinary incontinence, palpitations, dyspnoea and minor psychiatric disturbance.

Other effects
In one trial a significant fall in blood sugar was reported, though values remained close to normal and no symptoms of hypoglycaemia occurred.[4]

Interference with clinical pathology tests
None has been reported.

High risk groups

Neonates
There is no information on the use of carbocisteine in neonates or infants and no recommended dosage schedule.

Breast milk. There is no information on the use of carbocisteine during lactation.

Pregnant women
While there are no reports of teratogenic effects, the manufacturers do not recommend the use of carbocisteine in the first trimester.

The elderly
Many reported trials have included elderly patients and no special problems have arisen.

Concurrent disease
No special precautions are recommended by the manufacturer, but it would seem sensible to avoid carbocisteine in patients with recent gastrointestinal bleeding.

Drug interactions

Neither hazardous nor therapeutically useful interactions have been reported.

Major outcome trials

1. Edwards G F, Steel A E, Scott J K, Jordan J W 1976 S-carboxymethylcysteine in the fluidification of sputum and treatment of chronic airway obstruction. Chest 70: 506–513

A double-blind, controlled trial of 82 patients with mild chronic bronchitis given carbocisteine 3 g daily for three months reported increased sputum volume, reduced sputum viscosity and improved lung volume.

2. Puchelle E, Aug F, Polu J M 1978 Effect of muco-regulator S-carboxymethylcysteine in patients with chronic bronchitis. European Journal of Clinical Pharmacology 14: 177–184

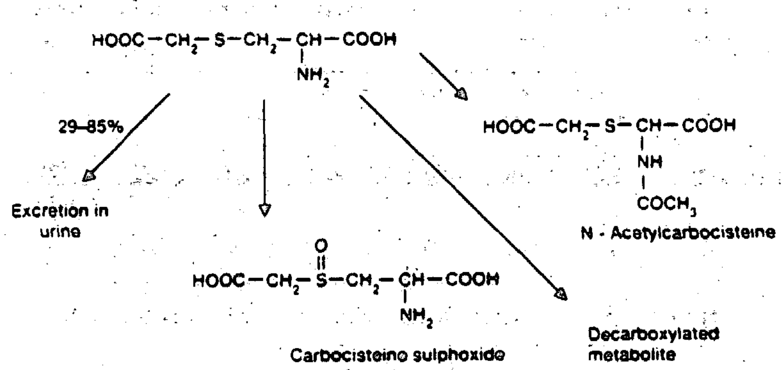
A double-blind study of 20 patients with chronic bronchitis given carbocisteine 3 g daily for 2 weeks reported improvement in cough, ease of expectoration and ausculatory findings, but with an increase in sputum viscosity and no change in lung volumes.

The variation in reported effects of carbocisteine in chronic bronchitis and otitis media has been detailed in the section on clinical pharmacology.

References

1. Havez R, Degand P, Roussel P, Randoux A 1970 Mode d'action biochemique des derives de la cysteine sur le mucus bronchique. Poumon Coeur 26: 81–90
2. Medici T C, Radielovic P 1979 Effects of drugs on mucus glycoproteins and water in bronchial secretion. Journal of International Medical Research 7: 434–442
3. Edwards G F, Steel A E, Scott J K, Jordan J W 1976 S-carboxymethylcysteine in the fluidification of sputum and treatment of chronic airway obstruction. Chest 70: 506–513
4. Puchelle E, Aug F, Polu J M 1978 Effect of muco-regulator S-carboxymethylcysteine in patients with chronic bronchitis. European Journal of Clinical Pharmacology 14: 177–184

Fig. 1 Metabolism of carbocisteine



EXTRACTED FOR PERIOD: 01/07/63 - 06/10/95 EARLIEST REACTION DATE: 20/04/73 REACTION: ALL ORIGIN: UK

DRUG : CARBOCISTEINE ROUTE: ALL SUBSTANCE/VARIANT/NPCG SUBS

SINGLE-CONSTITUENT PRODS : [redacted]

MULTI-CONSTITUENT PRODS : NONE

SYSTEM ORGAN CLASS / HIGH LEVEL TERM / REACTION NAME	SINGLE CONST TOT	SINGLE CONST FTL	MULTI CONST TOT	MULTI CONST FTL
Cardiovascular disorders				
Cardiovascular disease symptoms & signs				
Oedema	2	0	0	0
Cardiac arrhythmias (general)				
Tachycardia NOS	1	0	0	0
SYS ORGAN CLASS TOTAL:	3	0	0	0
Disorders of the ear				
Miscellaneous ear disorders				
Tinnitus	1	0	0	0
Vestibular disorders				
Vertigo	1	0	0	0
SYS ORGAN CLASS TOTAL:	2	0	0	0
Disorders of the immune system				
Allergies (exc angioedema)				
Allergic reaction NOS	1	0	0	0
SYS ORGAN CLASS TOTAL:	1	0	0	0
Gastrointestinal disorders				
Anal & rectal disorder NOS				
Rectal haemorrhage	1	0	0	0
Enteritis, colitis & proctitis (exc infections)				
Colitis	1	0	0	0
Gastrointestinal system symptoms & signs				
Abdominal pain NOS	2	0	0	0
Diarrhoea NOS	4	0	0	0
Haematemesis	2	0	0	0
Melaena	1	0	0	0
Nausea	1	0	0	0
Vomiting	4	0	0	0
Tongue disorders				
Glossitis	1	0	0	0
Ill-defined gastrointestinal infections				
Gastroenteritis NOS	1	0	0	0
Upper gastrointestinal ulceration & perforation				
Duodenal ulcer	1	0	0	0
Duodenal ulcer haemorrhage	1	0	0	0
Gastritis	1	0	0	0
Oral soft tissue disorders				
Stomatitis ulcerative	1	0	0	0
Salivary gland disorders				
Salivary gland enlargement NOS	1	0	0	0
SYS ORGAN CLASS TOTAL:	23	0	0	0
General disorders				
General symptoms & signs				
Dizziness (exc vertigo)	1	0	0	0
Fatigue	3	0	0	0
Hyperkinetic syndrome	2	0	0	0
Influenza like illness	1	0	0	0
Insomnia	2	0	0	0
Irritability	3	0	0	0
Malaise	2	0	0	0
Nightmares	5	0	0	0
Pain	1	0	0	0
Pyrexia	1	0	0	0
Screaming	1	0	0	0
Sedation	3	0	0	0
Therapeutic & non-therapeutic drug responses				
Drug interaction NOS	3	0	0	0
SYS ORGAN CLASS TOTAL:	28	0	0	0
Haemopoietic disorders				
Clotting & coagulation defects (exc platelets)				
Prothrombin decreased	1	0	0	0
Disorders with decreased white blood cells				
Neutropenia	1	0	0	0
SYS ORGAN CLASS TOTAL:	2	0	0	0
Musculoskeletal, connective tissue & bone disorders				
Muscle disorders				
Myalgia	2	0	0	0
Arthropathies nonspecific				
Arthralgia	1	0	0	0
Crystal arthropathies				
Gout	1	0	0	0
SYS ORGAN CLASS TOTAL:	4	0	0	0
Neurological disorders				
Altered consciousness				
Syncope	1	0	0	0
Convulsions & epilepsy				

ANNEX IV

MCA - ADROIT DRUG ANALYSIS PRINT (ANR010) DRUG : CARBOCISTEINE

EXTRACT PERIOD: 01/07/63 - 06/10/95 S/V/N: SUBS REACTION: ALL RTE: ALL ORIGIN: UK DATE: 06/10/95

SYSTEM ORGAN CLASS / HIGH LEVEL TERM / REACTION NAME	SINGLE CONST TOT	SINGLE CONST FTL	MULTI CONST TOT	MULTI CONST FTL
Convulsions NOS	1	0	0	0
Epilepsy aggravated	1	0	0	0
Headache (all forms)				
Headache NOS	3	0	0	0
Migraine	1	0	0	0
Sensory abnormalities				
Sensory disturbance NOS	1	0	0	0
SYS ORGAN CLASS TOTAL:	8	0	0	0
Psychiatric disorders				
Affective disorders (all forms)				
Depression NOS	3	0	0	0
Psychiatric symptoms & signs				
Aggression	2	0	0	0
Emotional problems	2	0	0	0
Hallucinations	3	0	0	0
Nervousness	1	0	0	0
SYS ORGAN CLASS TOTAL:	11	0	0	0
Renal & urinary disorders				
Urinary disease symptoms & signs				
Urinary incontinence	1	0	0	0
Renal failure (all forms)				
Renal failure NOS	1	0	0	0
SYS ORGAN CLASS TOTAL:	2	0	0	0
Reproductive disorders				
Female reproductive tract infections				
Vulvovaginitis	1	0	0	0
SYS ORGAN CLASS TOTAL:	1	0	0	0
Respiratory disorders				
Respiratory symptoms & signs				
Dyspnoea	1	0	0	0
Nasal cavity & sinus disorders (exc infections)				
Epistaxis	2	0	0	0
Rhinitis NOS	1	0	0	0
SYS ORGAN CLASS TOTAL:	4	0	0	0
Skin & subcutaneous tissue disorders				
Bullous dermatoses				
Blister	1	0	0	0
Dermatitis & eczema				
Dermatitis NOS	1	0	0	0
Dermatitis lichenoid	1	0	0	0
Exfoliative dermatitis NOS	1	0	0	0
Localised exfoliation	1	0	0	0
Miscellaneous skin & subcutaneous tissue disorders				
Pruritus	4	0	0	0
Photosensitivity eruptions				
Photosensitivity reaction	1	0	0	0
Pigmentation disorders				
Skin depigmentation	1	0	0	0
Rashes				
Rash NOS	14	0	0	0
Rash erythematous	8	0	0	0
Rash maculo-papular	8	0	0	0
Rash morbilliform	2	0	0	0
Sweating disorders				
Sweating increased	1	0	0	0
Vascular abnormalities of skin				
Petechiae	1	0	0	0
Purpura	2	0	0	0
Angioedema				
Angioedema	1	0	0	0
Face oedema	2	0	0	0
Giant urticaria	1	0	0	0
Urticaria				
Urticaria	14	0	0	0
SYS ORGAN CLASS TOTAL:	64	0	0	0
TOTAL REACTIONS FOR DRUG:	153	0	0	0

TOTAL REPORTS: 119 TOTAL FATAL OUTCOME: 0

*** END OF REPORT ***

CRITERIA FOR CLASSIFYING MEDICINAL PRODUCTS AS PRESCRIPTION-ONLY MEDICINES.

(Directive 92/26/EEC and Section 58A of The Medicines Act 1968)

1. Prescription control is applied to any product which

- is likely to present a direct or indirect danger to human health, even when used correctly, if used without the supervision of a doctor or dentist; or

- is frequently and to a very wide extent used incorrectly, and as a result is likely to present a direct or indirect danger to human health; or

- contain substances or preparations of substances of which the activity requires, or the side effects require, further investigation; or

- is normally prescribed by a doctor or dentist for parenteral administration.

2. In deciding whether the above apply, account should be taken of whether the product

(a) contains a substance which is listed in any of Schedules I,II or IV to the Narcotic Drugs Convention (where the product is not a preparation listed in Schedule III to that Convention): or

(b) contains a substance which is listed in any of Schedules I,II or IV of the Psychotropic Substances Convention (where the product is not a preparation which may be exempted from measures of control in accordance with paragraphs 2 and 3 of article 3 of that Convention): or

(c) is likely, if incorrectly used-

(i) to present a substantial risk of medicinal abuse, or
(ii) to lead to addiction, or
(iii) to be used for illegal purposes: or

(d) contains a substance which, by reason of its novelty or properties, might fall within paragraph (c) above but as to which there is insufficient information available to determine whether it does so fall: or

(e) by reason of its pharmaceutical characteristics or novelty, or in the interests of public health, is reserved for treatments which can only be followed in a hospital: or

(f) is used in the treatment of conditions which must be diagnosed in a hospital or in an institution with special diagnostic facilities (although administration and subsequent supervision may be carried out elsewhere): or

(g) is intended for outpatients but may produce very serious side-effects which would require a prescription drawn up as required by a specialist and special supervision throughout the treatment.

3. Exemptions from prescription control may be made having regard to-

(a) the maximum single dose;
(b) the maximum daily dose;
(c) the strength of the product;
(d) its pharmaceutical form;
(e) its packaging; or
(f) such other circumstances relating to its use as may be specified in the determination.

ANNEX V(ii)

Aide-memoir on making POM to P Switches

1. In January 1993, the Medicines Act was amended to include the criteria for prescription control as laid down in Council Directive 92/26/EEC which states that medicinal products shall be classified as prescription-only medicines where they:

   - are likely to present a danger either directly or indirectly, even when used correctly, if utilized without medical supervision, or

   - are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health, or

   - contain substances or preparations thereof the activity and/or side effects or which require further investigation, or

   - are normally prescribed by a doctor to be administered parenterally.

2. To confirm that a drug/product is suitable for switching from POM to P, the following should all apply:

   - the indication(s) for the drug/product must be suitable for self medication including self diagnosis of the condition which may be a recurrent attack of a condition which required a physician-aided diagnosis on first attack,

   - in the doses recommended, the drug/product has an acceptable margin of safety during unsupervised use including safety in overdose or following accidental misdiagnosis of the condition by the patient,

   - the drug/product is not a new chemical entity for which further post-marketing experience of safety is considered desirable,

   - the drug/product does not present a hazard to the community (i.e. indirect danger) from unsupervised use as might occur with the development of resistant flora to antibiotics

   - the drug/product has no major abuse or dependence potential

   - the drug product is not for parenteral use.

3. The refusal of a request for reclassification from POM to P requires the applicant to be informed as to which of the POM criteria still apply.