DEPARTMENT OF HEALTH & HUMAN SERVICES

DOCUMENT # 18012

Public Health Service

Food and Drug Administration
Rockville MD 20857

OCT 29 1981

FOI Services Incorporated
12315 Wilkins Avenue
Rockville, MD 20852

In reply refer to
File FOI-25739
Your Control No. 18012

Dear Sir:

This is in reply to your letter of October 9, 1981, received by this division on October 20, 1981, in which you requested information concerning Mucomyst Solution, NDA 13-601.

Enclosed is the information you requested.

As you will note, minor deletions have been made in the record(s) furnished to you. In the judgement of the Food and Drug Administration the information deleted does not fall within the scope of your request and, in any case, is not required to be disclosed under the Freedom of Information Act. If, however, you do desire to review the deleted material, please make an additional request. If the agency should deny you this information, you have the right to appeal such denial to the Department of Health and Human Services. Any letter of denial will tell you how to make this appeal.

Sincerely yours,

Gary H. Boyer

Gary H. Boyer
Freedom of Information Officer
Division of Surgical-Dental
Drug Products
Bureau of Drugs

OCT 29 1981

NDA 13-001

SEP 14 1963

Mead Johnson & Company
Attention: Dr. Byron B. Clark
Vice President, Research Center
Evansville 21, Indiana

Gentlemen:

Reference is made to your new drug application dated May 17, 1962 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation "Acetylcysteine."

We also acknowledge receipt of your additional communication dated August 23, 1963, amending the application.

The application was filed on August 27, 1963.

We have completed our study of this application and it is approved.

Under the provisions of section 505(j) of the Act and section 130.13 of the regulations, records of clinical and other experience with the drug are to be maintained and reported to the Division of New Drugs in triplicate as follows:

(1) Immediately upon its receipt by you, information concerning any mixup of the drug or its labeling with another article and information regarding any bacteriological, significant chemical, physical, or other change or deterioration in the drug or any failure of one or more distributed batches of the drug to meet the specifications established for it in the new drug application.

(2) Within fifteen working days of their receipt by you, reports concerning any unexpected side effect, injury, toxicity, or sensitivity reaction or any unexpected incidence or severity thereof that is associated with clinical or other use of the drug, whether or not such effect has been determined to be attributable to the drug; and reports of any unusual failure of the drug to exhibit its expected pharmacological activity.

(3) Within intervals of three months during the first year beginning with the date of approval of this application, six months during the second year following such date, and at yearly intervals

thereafter: (1) All other information on clinical and other experience, studies, investigations, and tests conducted, received, or otherwise obtained by you; (2) Copies of all mailing pieces and other labeling for the drug; and (3) Copies of all advertising used in promoting the drug.

If any such reports have come to you since the submission of the new drug application, we are requesting that you promptly submit information about them. We assume that the application contains all such data to the date of its submission to us, but if it does not it should be supplemented with the data.

If additional information is not available at the intervals specified, a statement to this effect should be submitted. Failure to maintain and submit such records may be the basis for regulatory action or withdrawing the approval of the application.

The printed brochure-package insert accompanying your communication of August 23, 1963 is not identical to the draft copy incorporating the changes recommended by our letter of August 2, 1963. We note that the text has generally included the changes which we had recommended. We also have noted the typographical errors listed on page 2533a, together with your commitment that they will be corrected prior to your use of this labeling. The changes are not considered objectionable, and do not preclude approval of the application. However, our approval is contingent upon the following revision and augmentation of the "WARNINGS" section of the final printed brochure-insert:

The entire "WARNINGS" section should appear in bold face type.

The "WARNINGS" section should state, in a separate (second) following paragraph: Asthmatics under treatment with Mucomyst (Acetylcysteine) should be watched carefully. If bronchospasm occurs, this medication should be immediately discontinued.

We urge that in your reprinting of the brochure-insert a larger, and consequently more legible, type size will be used.

Please forward five copies of the corrected printed brochure-insert, in the format intended for use in the finished market packages of the drug, when available.

Sincerely yours,

John D. Lockhart, M.D.
Medical Officer
Division of New Drugs
Bureau of Medicine

SUMMARY of NDA 13-601

Mead Johnson Company
Evansville, Indiana

Product: Acetylcysteine, 20%
(1-acetamido-1-carboxy-ethane-2-thiol)

Product 5052-6S	
Acetylcysteine	20.0%
Disodium EDTA	.05%
NaOH for pH to 7	4.9%
Deionized HOH qs to	100.0%

Acetycysteine is offered as a mucolytic agent for the relief of mucous and mucopurulent pulmonary secretions, especially those found as bronchiolar plugs, as in fibrocystic disease. It is proposed as an adjunct in the therapy of diseases whose symptoms include viscid or inspissated mucus.

Recommended dose: 1 to 10 ml., via a face mask or mouthpiece (aerosolized), or up to 300 ml. into a tent or croupette over a period of hours, and for intratracheal use, in full or diluted strengths.

Acetylcysteine comes in plastic-stoppered glass vials containing 10 ml. or 30 ml., and in glass ampuls containing 10 ml.

Pharmacologic Studies:

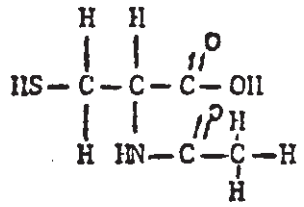
Acute Toxicity - LD_{50} (mg/kg)

Mice -	I.V.	1200,	Oral	3000+		
Guinea pigs -	"	1550,			I.P.	1500
Rats -			"	5500,	"	1600
Dogs -	"	700,	"	1000+		

Subacute Toxicity and Chronic Toxicity - The originally submitted NDA reported Guinea pigs - Aerosol (3-)18% daily (up to) 8 weeks caused death in 7/12 vs N saline 1/6, with bronchopneumonia and/or pleurisy in the majority of both drug and N saline groups.+ A subsequent (Jan., 1963) five-week inhalation toxicity study of dogs, rats, and rabbits showed no alterations in blood picture, liver, or kidney function; however, pneumonitis was noted in the lungs of all species. Still more recent studies (March and May, 1963) outline a 3-week inhalation toxicity and drug-withdrawal study in 60 albino rats; pulmonary changes amont Acetylcyste treated rats were not significantly different from those found among rats exposed to identical aerosol sprays of either distilled water or 0.9% sodium chloride solution. Similar results were found in a 12 week rat, rabbit, and guinea pig test; i.e., the chilling effect of the spray was felt to be responsible for pneumonitis, and no other gross or histopathological effects from the drug were found. In January, 1963, the

Division of Pharmacology was satisfied with the lack of pulmonary pathology, ciliary dysfunction, and sulfhemoglobin production as well as with H_2S non-toxicity. (Toxic concentration well under 1:200,000) A February, 1963 communication from the Company also answered in detail some of Dr. 's questions, including Cystine excretion studies, Sulfhemoglo studies, H_2S reports, and ciliary activity data.

Metabolic Studies:



The free sulfhydryl group in the molecule presumed to split disulfide bonds in mucus (mucoproteins) and lower viscosity. End-products of absorption, acetate, and cysteine, are handled as normally occurring metabolic products.

In vitro mucolytic effect well demonstrated.

Clinical Studies:

Originally, 8 investigators and over 700 cases, but not all of these pulmonary. Dr. presented reports on 27 patients (26 with cystic fibrosis), six months to 22 years, 25 of whom were helped, as evidenced by easier cough and breathing, thinner more copious mucus. His work tends to be thorough and detailed, although Dr. feels that these children were not fully stabilized (i.e., on antibiotics, enzymes, mist, etc.) before acetylcysteine therapy was begun. (Tel. conversation, March, 1963.) Also in the original NDA, Dr. reported on 34 patients, with various pulmonary diseases, treated for short times (8 - 10+ days) with acetylcysteine, and made comments such as "improvement in cough" on most of the records. Dr. reported on 157 patients, 91 of whom were post-operative, 18 others with tracheostomi This large group received acetylcysteine for periods ranging from several days to several weeks and were benefited by the "thinner mucus," "easier cough," lower incidence of post-op. atelectasis.

On March 7, 1963, considerable data were submitted, pertaining to chest x-ray findings as follows: Dr. submitted x-ray reports and actual x-ray photographs on 16 patients who had been on acetylcysteine therapy for from 3 to 324 days. Dr submitted serial x-ray reports on 49 patients, to show that acetylcysteine had not been a causative factor in pneumonitis. Older data on and 's patients was also summarized to show this. Statements from and pertained to the lack of pneumonitis due to acetylcysteine. The March submission also contained a short but careful study by This was the last actual pulmonary function study in the NDA. He analyzed 28 patients with cystic fibrosis, classified as moderate, severe, or fatal.

After a six week control period (perhaps in answer to the "not stabilized" criticism by other C-F workers), these children were treated for from 10 - 118 weeks with acetylcysteine aerosol twice daily. Results of spirometer were analyzed. There was an overall 53% improvement in the therapy, but the patients with restrictive lung disease improved less than those with obstructive disease.

Also included in the March submission are six references on the mucolytic effectiveness of acetylcysteine, and additional clinical data from 45 investigators, of varying quality. (Some testimonial, some careful clinical reports.)

On April 11, 1963, Dr. of Mead Johnson had a discussion with Drs. and to discuss progress of the NDA. Possibility of more pulmonary function tests was discussed. Lack of improvement of many asthmatics on acetylcysteine, in fact, irritating effect, also brought out. Use of intratracheal instillation promising. Suggested study: (on asthmatics) controls, bronchodilators alone, bronchodilators and acetylcysteine, possible acetylcysteine alone.

On July 3, 1963, a new submission was offered, with the following contents: A review of data, including in vitro studies, and up-to-date in vivo clinical studies, by Drs. an These total over 372 patients, all pulmonary. A new brochure is included, in which caution is urged in the use of acetylcysteine in asthmatics. The investigational data is summarized and well organized, and the physician is shown leeway in the method of use of acetylcysteine, depending on the patient's condition. It is brought out, for the first time, that acetylcysteine is chemically compatible with, and may be mixed in solution with, vasoconstrictors, x-ray contrast media, bronchodilators and some topical anesthetics; however, it is incompatible in solution with tetracycline, oxytetracycline, and oleandomycin phosphate. Data to support this is lacking

The new submission also includes 94 new clinical studies, by 20 investigators (some new). The use of the acetylcysteine ranges from hours to years (intermittently) and in ages from newborns (respiratory distress syndrome) to aged and terminally ill pulmonary cripples. The variation in the results seems to depend on how much the mucous obstruction contributes to the respiratory difficulty, and on the patients ability to cough up the more liquid mucus. In fact, this last factor is a distinct danger in those not accustomed to using effective mucolytic agents, and is brought out as a Caution in the brochure. Side effects include the slightly nauseating hydrogen sulfide smell, and the objection to the slightly more stimulated cough urge, which some patients tried to repress due to the pain of coughing.

Additional in vitro and in vivo laboratory studies are also included in the new submission, as is stability data, pathology reports, recall information, and reprints, some new.

Literature reviewed:

Stein, Myron, et al. Pulmonary Evaluation of Surgical Patients. JAMA 181:765. Sept. 1, 1962. ("The maximal expiratory flow-rate determination was the most effective presurgical test.")

Lieberman, Jack, et al. Proteolytic Enzyme Activity and the Role of Desoxyribose Nucleic Acid in Cystic Fibrosis Sputum. Pediatrics 31:1030, June, 1963.

Mitchell, Robert A. Pulmonary Function and Tests For Ventilatory Adequacy. Anesthesiology 23:422. July-August, 1962.

Lovejoy, Frank W. et al. Aerosols, Bronchodilators and Mercolytic Agents. Anesthesiology 23:46. July-August, 1962.

Labeling:

Claims adequately substantiated, either by laboratory investigation or clinical studies, in some cases by publications. Adverse effects, though few, adequately delineated. Limitations of therapy spelled out. Procedure of administration well described. Supporting data needed on incompatibilit

Conclusions:

I have no more reservations about the safety of acetylcysteine, and it is approvable on that score. Effectiveness, for the uses it is intended for and labeled for, is also substantiated. In this instance, the drug in question is intended as an adjunct in life-threatening or chronically and progressively debilitating bronchopulmonary disease, and should be available to the physician. I feel its most promising use will be in the ve condition in which mucoid impactions on bronchioles are most viscid; fibrocystic disease.

M. D.

UTION FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION

MUCOMYST®
(ACETYLCYSTEINE)

U.S. Patent No. 3,091,569

SEP 0 1 1978

IPTION Acetylcysteine is the nonproprietary name for the N-acetyl derivative of urally occurring amino acid, L-cysteine. Chemically, it is N-acetyl-L-cysteine.
compound is a white crystalline powder which melts at 104–110°C and has a ight odor. It has a molecular weight of 163.2. The agent is supplied in vials ing a 10% or 20% solution of acetylcysteine as the sodium salt.

NS The viscosity of pulmonary mucous secretions depends on the concentrations oprotein and to a lesser extent deoxyribonucleic acid (DNA). The latter increases ncreasing purulence owing to cellular debris. The mucolytic action of acetyl- e is related to the sulfhydryl group in the molecule. This group probably "opens" e linkages in mucus thereby lowering the viscosity. The mucolytic activity of ysteine is unaltered by the presence of DNA, and increases with increasing pH. ant mucolysis occurs between pH 7 and 9.

ATIONS Mucomyst (acetylcysteine) is indicated as adjuvant therapy for patients normal viscid, or inspissated mucous secretions in such conditions as:
onic bronchopulmonary disease (chronic emphysema, emphysema with bronchitis, chronic asthmatic bronchitis, tuberculosis, bronchiectasis and primary amyloidosis of the lung)
te bronchopulmonary disease (pneumonia, bronchitis, tracheobronchitis)
monary complications of cystic fibrosis
heostomy care
monary complications associated with surgery
during anesthesia
-traumatic chest conditions
ectasis due to mucous obstruction
nostic bronchial studies (bronchograms, bronchospirometry, and bronchial wedge catheterization)

RAINDICATIONS – Mucomyst (acetylcysteine) is contraindicated in those who are sensitive to it.

NGS After proper administration of acetylcysteine, an increased volume of l bronchial secretions may occur. When cough is inadequate, the open airway maintained by mechanical suction if necessary. When there is a large mechanical ue to foreign body or local accumulation, the airway should be cleared by cheal aspiration, with or without bronchoscopy.
rgatics under treatment with Mucomyst (acetylcysteine) should be watched ; if bronchospasm progresses, this medication should be immediately oped.

UTIONS With the administration of acetylcysteine, the patient may initially slight disagreeable odor which soon is not noticeable. With a face mask there a stickiness on the face after nebulization which is easily removed by washing ter.
r certain conditions, a color change may take place in the solution of steine in the opened bottle. The light purple color is the result of a chemical which does not significantly impair the safety or mucolytic efficacy of steine.
inued nebulization of an acetylcysteine solution with a dry gas will result in an d concentration of the drug in the nebulizer because of evaporation of the Extreme concentration may impede nebulization and efficient delivery of the lution of the nebulizing solution with Sterile Water for Injection, U.S.P., as ation occurs, will obviate this problem.

ADVERSE EFFECTS – Adverse effects have included stomatitis, nausea and rhinorrhea. Sensitivity and sensitization to Mucomyst have been reported very rarely. A few susceptible patients, particularly asthmatics (see Warnings), may experience varying degrees of bronchospasm associated with the administration of nebulized acetylcysteine. Most patients with bronchospasm are quickly relieved by the use of a bronchodilator given by nebulization.

DOSAGE AND ADMINISTRATION – Mucomyst (acetylcysteine) is available in plastic stoppered glass vials containing 10 ml. or 30 ml. The 20% solution may be diluted to a lesser concentration with either sterile normal saline or Sterile Water for Injection, U.S.P. The 10% solution may be used undiluted.

Nebulization – face mask, mouth piece, tracheostomy
When nebulized into a face mask, mouth piece, or tracheostomy, 1–10 ml. of the 20% solution or 2–20 ml. of the 10% solution may be given every 2–6 hours; the recommended dose for most patients is 3–5 ml. of the 20% solution or 6–10 ml. of the 10% solution 3 to 4 times a day.

Nebulization – tent, Croupette
In special circumstances it may be necessary to nebulize into a tent or Croupette, and this method of use must be individualized to take into account the available equipment and the patient's particular needs. This form of administration requires very large volumes of the solution, occasionally as much as 300 ml. during a single treatment period. If a tent or Croupette must be used, the recommended dose is the volume of solution (using 10% or 20% acetylcysteine) that will maintain a very heavy mist in the tent or Croupette for the desired period. Administration for intermittent or continuous prolonged periods, including overnight, may be desirable.

Direct Instillation
When used by direct instillation, 1–2 mL of a 10 to 20% solution may be given as often as every hour.

When used for the routine nursing care of patients with tracheostomy, 1 to 2 mL of a 10 to 20% solution may be given every 1 to 4 hours by instillation into the tracheostomy.

Acetylcysteine may be introduced directly into a particular segment of the bronchopulmonary tree by inserting (under local anesthesia and direct vision) a small plastic catheter into the trachea. Two to 5 ml. of the 20% solution may then be instilled by means of a syringe connected to the catheter.

Acetylcysteine may also be given through a percutaneous intratracheal catheter. One to 2 ml. of the 20% or 2–4 ml. of the 10% solution every 1 to 4 hours may then be given by a syringe attached to the catheter.

Diagnostic Bronchograms
For diagnostic bronchial studies, 2 or 3 administrations of 1 to 2 ml. of the 20% solution or 2–4 ml. of the 10% solution should be given by nebulization or by instillation intratracheally, prior to the procedure.

ADMINISTRATION OF AEROSOL
Materials
Mucomyst may be administered using conventional nebulizers made of plastic or glass. Certain materials used in nebulization equipment react with acetylcysteine. The most reactive of these are certain metals (notably iron and copper) and rubber. Where materials may come into contact with acetylcysteine solution, parts made of the following acceptable materials should be used: glass, plastic, aluminum, anodized aluminum, chromed metal, tantalum, sterling silver, or stainless steel. Silver may become tarnished after exposure, but this is not harmful to the drug action nor to the patient.

Nebulizing Gases
Compressed tank gas (air) or an air compressor should be used to provide pressure for nebulizing the solution. Oxygen may also be used but should be used with usual caution in patients with severe respiratory disease and CO_2 retention.

APPARATUS Mucomyst (acetylcysteine) is usually administered as fine nebulae for its local effect, and the nebulizer used should be capable of providing optimal quantities of a suitable range of particle sizes.

The selection of apparatus for nebulization depends upon the desired particle size and rate of administration. Commercially available nebulizers will produce nebulae of acetylcysteine satisfactory for retention in the respiratory tract. Most of the nebulizers tested will supply a high proportion of the drug solution as particles of less than 10 microns in diameter. Mitchell[a] has shown that a range of particle size up to 10 microns should be satisfactorily retained in the respiratory tract.

Units that nebulized acetylcysteine with a satisfactory efficiency were the Mast Myst Nebulizer (Mead Johnson Pharmaceutical Division, Evansville, Indiana), Mist-O_2-Gette ET-I-T (Mist O_2 Gen Equipment Co., 2711 Adeline St., Oakland, Calif.), De Vilbiss 42 (The De Vilbiss Co., Somerset, Pa.), and Vaponefrin Standard Plastic Nebulizer (Vaponefrin Co., Division U.S. Vitamin & Pharmaceutical Corporation, 800 Second Avenue, New York, New York). Other units tested performed with equivalent or lesser efficiency of nebulization.

Hand bulbs may be used but are not recommended for routine use for nebulizing Mucomyst (acetylcysteine) because their output is generally too small. Some hand-operated nebulizers deliver particles that are larger than optimum for inhalation therapy.

Heated (hot pot) Nebulizer
Mucomyst should not be placed directly into the chamber of a heated (hot pot) nebulizer. A heated nebulizer may be part of the nebulization assembly to provide a warm saturated atmosphere if the Mucomyst aerosol is introduced by means of a separate unheated nebulizer. Usual precautions for administration of warm saturated nebulae should be observed.

The nebulized solution may be breathed directly from the nebulizer. Nebulizers may also be attached to plastic face masks, plastic face tents, plastic mouth pieces, conventional plastic oxygen tents, or head tents. Suitable nebulizers may also be fitted for use with the various intermittent positive pressure breathing (IPPB) machines.

The nebulizing equipment should be cleaned immediately after use; the residues may occlude the fine orifices or corrode metal parts.

Prolonged Nebulization
When three-fourths of the initial volume of acetylcysteine solution has been nebulized, a quantity of Sterile Water for Injection, U.S.P. (approximately equal to the volume of solution remaining) should be added to the nebulizer. This obviates any concentration of the agent in the residual solvent remaining after prolonged nebulization.

Storage of Opened Vials
If only a portion of the solution in the vial is used, to minimize contamination the remainder should be stored in a refrigerator and used within 96 hours.

COMPATIBILITY The physical and chemical compatibility of acetylcysteine solutions with other drugs commonly administered by nebulization, direct instillation, or topical application, has been studied.

Acetylcysteine should not be mixed with all antibiotics. For example, the antibiotics tetracycline hydrochloride, oxytetracycline hydrochloride, and erythromycin lactobionate were found to be incompatible when mixed in the same solution. These agents may be administered from separate solutions if administration of these agents is desirable.

a. Amer. Rev. Resp. Dis. 82:627-639, 1960.

VITRO COMPATIBILITY[1] TESTS OF ACETYLCYSTEINE

PRODUCT AND/OR AGENTS	MANUFACTURER (TRADEMARK)	COMPATIBILITY RATING	RATIO TESTED[2] ACETYLCYSTEINE	RATIO TESTED[2] PRODUCT OR AGENT
ESTHETIC, GAS				
...ane USP	Aspen Pharmacal	Compatible	20%	Infinite
...ous Oxide USP	National Cylinder Gas Company	Compatible	20%	Infinite
ESTHETIC, LOCAL				
...ine HCl	Merck	Compatible	10%	5%
...caine HCl	Astra Pharmaceutical	Compatible	10%	2%
...caine HCl	Winthrop Laboratories	Compatible	10%	1%
BACTERIALS	All parenteral forms of each antibiotic were used			
...cillin	Upjohn	Compatible	10%	5,000 Unit
...cillin	Lilly, Abbott	Compatible	10%	40 mg/ml
...mycin	Parke, Davis (Chloromycetin)	Compatible	20%	20 mg/ml
...mycin	Ayerst Laboratories	Compatible	10%	125 mg/ml
...mycin	Schering Corporation	Compatible	10%	20 mg/ml
...mycin	Bristol Laboratories	Compatible	10%	167 mg/ml
...mycin	Upjohn	Compatible	17%	85 mg/ml
...mycin	Upjohn (Kantrex)	Compatible	10%	150 mg/ml
...mycin	Eli Lilly (Mallinckrodt)	Compatible	10%	100 mg/ml
...cillin G	Parke, Davis	Compatible	10%	25 mg/ml
...cillin G	Lederle Laboratories	Compatible	10%	25,000 Unit
...cillin G	Wellcome Laboratories	Compatible	10%	100,000 Unit
...cillin G	Bristol Laboratories	Compatible	10%	50,000 Unit
...cillin	Bristol Laboratories	Compatible	10%	87.5 mg/ml
...cillin	Lilly, Abbott	Compatible	10%	100 mg/ml
...cillin	Warner Chilcott (Kelly-Wyeth)	Compatible	10%	37.5 mg/ml
...cillin	Lilly, Pfizer	Compatible	10%	25 mg/ml
...cillin	Squibb	Incompatible	4.15%	1.04 mg/ml
...cycline HCl	Lederle, Pfizer	Incompatible	10%	12.5 mg/ml
...cycline HCl	Abbott	Incompatible	10%	25 mg/ml
	Erythrocin Lactobionate-IV			
...cycline HCl	Pfizer (Terramycin IV)	Incompatible	10%	12.5 mg/ml
...cillin	Bristol (Polycillin)	Incompatible	10%	50 mg/ml
...cillin	Lederle (Achromycin)	Incompatible	10%	12.5 mg/ml

IN VITRO COMPATIBILITY[1] TESTS OF ACETYLCYSTEINE

PRODUCT AND/OR AGENTS	MANUFACTURER (TRADEMARK)	COMPATIBILITY RATING	RATIO TESTED[2] ACETYLCYSTEINE	RATIO TESTED[2] PRODUCT OR AGENT
BRONCHODILATORS				
Isoproterenol HCl		Compatible	2.5%	0.5%
Isoproterenol HCl		Compatible	10%	0.05%
Isoproterenol HCl		Compatible	20%	0.05%
Isoproterenol HCl	Winthrop Isuprel HCl	Compatible	13.3%	33%
			0 part	11 part
Aerobron Compound	Lilly	Compatible	13.3%	
			0 part	11 part
Bronkosol	Boots	Compatible	13.3%	
			0 part	11 part
Epinephrine HCl	Parke, Davis (Adrenalin HCl 1:1000)	Compatible	13.3%	33%
			0 part	11 part
CONTRAST MEDIA				
Iodized Oil USP	Ferguson Specialties	Incompatible	20%/20 ml	40%/10 ml
DECONGESTANTS				
Phenylephrine HCl		Compatible	5.0%	25%
Phenylephrine HCl	Winthrop Sinus-Synephrine HCl Nasal Solution, 0.5%	Compatible	13.3%	17%
			0 part	11 part
ENZYMES				
Pancreatic Dornase (use and use at once)	Merck (Dornase)	Compatible	10.7%	5,000 Unit
Chymotrypsin	Armour	Incompatible	3%	400 γ/ml
Trypsin	Armour	Incompatible	5%	400 γ/ml
SOLVENTS				
Alcohol		Compatible	12%	10.28%
Propylene Glycol		Compatible	3%	10%
STEROIDS				
Dexamethasone 21-Phosphate	Merck (Decadron Phosphate)	Compatible	10%	0.8 mg/ml
Prednisolone 21-Phosphate	Merck (Hydeltrasol)	Compatible	10.7%	2.3 mg/ml
OTHER AGENTS				
Hydrogen Peroxide		Incompatible	Will retard	
Sodium Bicarbonate, U.S.P.		Compatible	20%	4.2%
			0 part	11 part

[1] The rating, Incompatible, is based on the formation of a precipitate, a change in clarity, immiscibility, or a rapid loss of potency of acetylcysteine or the active ingredient of the PRODUCT AND/OR AGENT in the admixture.
The rating, Compatible, means that there was no significant physical change in the admixture when compared with a control solution of the PRODUCT AND/OR AGENT, and that there was no predicted chemical incompatibility. All of the admixtures have been tested for short-term chemical compatibility by assaying for the concentration of acetylcysteine after mixing.

[2] The active ingredient in the PRODUCT AND/OR AGENT was also assayed after mixing.
Some of the admixtures developed minor physical changes which were considered to be insufficient to rate the admixture incompatible. These are listed in footnotes 3, 4, and 5.

[3] A strong odor developed after storage for 24 hours at room temperature.

[4] The admixture was a slightly darker shade of yellow than a control solution of the PRODUCT AND/OR AGENT.

[5] A light tan color developed after storage for 24 hours at room temperature.

[6] Entries are final concentrations. Values in parentheses relate volumes of Mucomyst® solutions to volumes of test solutions.
The supplying of these data should not be interpreted as a recommendation for combining Mucomyst with other drugs. The table is not presented as positive assurance that no incompatibility will be present, since these data are based only on short-term compatibility studies done in the Mead Johnson Research Center. Manufacturers of drug products may change formulations. This could alter compatibilities. These data are intended to serve only as a guide for predicting compounding problems.
If it is deemed advisable to prepare an admixture, it should be administered as soon as possible after preparation. Do not store unused mixtures.

HOW SUPPLIED Mucomyst® 20% acetylcysteine solution. Sterile.

NDC 0087-0570-03	Cartons of three 10 ml. vials, 1 plastic dropper.
NDC 0087-0570-09	Cartons of three 30 ml. vials.
NDC 0087-0570-07	Cartons of twelve 4 ml. vials.

Mucomyst®-10 10% acetylcysteine solution. Sterile.

NDC 0087-0572-01	Cartons of three 10 ml. vials, 1 plastic dropper.
NDC 0087-0572-02	Cartons of three 30 ml. vials.
NDC 0087-0572-03	Cartons of twelve 4 ml. vials.

REFERENCES A bibliography on Mucomyst will be supplied on request.

Mead Johnson PHARMACEUTICAL DIVISION
MEAD JOHNSON & COMPANY · EVANSVILLE, INDIANA 47721 U.S.A.

 Date of Printing: May, 1978

assigned 6/1

TO : DIVISION OF NEW DRUGS
Attention: Dr. Ruskin

June 14, 1962

FROM : Division of Pharmacology
Dermal Toxicity

SUBJECT: Acetylcysteine (1-acetamido-1-carboxy-ethane-2-thiol)

NDA #13-601
Mead Johnson and Company, Evansville 21, Indiana (AF 7-711)

Acetylcysteine is offered as a mucolytic agent for the relief of mucus congestion associated with pulmonary disorders and diseases, (nasal congestion, and vaginal disorders of a purulent nature). The dose range recommended (2-1136 of NDA) is 1 to 10 ml of a 5% to 20% solution depending on clinical indication (once daily to 1X each 4 hours) by an intratracheal catheter or by aerosol in a croup tent or mask in pulmonary diseases. (Evidently the Manufacturer does not wish to offer the drug as an aid in nasal or vaginal congestion since no reference to these are made in the physicians brochure although clinical data has been submitted.)

Acute Toxicity: LD_{50} mg/kg at pH 7

Species	IV	IP	Oral
Mouse	1200	--	3000
Rat	--	2650 800 at pH 1.7	5100-6000
Dog	700		>1000
Guinea Pig	1550		1500

Subacute Toxicity:

24 Rats, Stomach tubed, 8 weeks 5 days per week dosage 100, 200, 400, 800, 1600 mg/kg/day. *,*1 Rats which were on 100 mg/kg dose were raised to a 1600 mg/kg dose after 2 weeks. There were no control animals for these groups of rats. Hematology was done on the 100 mg 800 mg and 1600 mg groups after two and eight weeks. The Hemograms were within normal limits. A slight depression and a slight anemia were noted at the 800 mg and 1600 mg levels. Growth was not effected.

Subacute Toxicity (continued)

Five animals died during study (1 respiratory, 1 accidental, 3 unknown-not autopsied). One animal developed opacity of the cornea and one developed labyrinthitis. Gross Pathology was negative. Microscopic pathology found no significant lesions in either group (800 or 1600 mg/kg) examined.

8 Dogs including 2 controls (males and females) orally, 2 x daily, 7 days/week for 8 weeks. Dosage - 80 mg/kg, 160 mg/kg, 320 mg/kg (2 dogs each). Hemograms were done pretreat, 4 and 8 weeks. Hemograms were predominately within normal limits except for high total leukocytes in two dogs. Growth and food consumption were in line with values of the controls. BUN values were normal SGOT and SGPT values were within normal ranges with one exception. Phenolsulfonphthalein excretion function was normal after 6.5 weeks on drug. Gross pathology-the liver of one high dose dog appeared ischemic and mottled. No microscopic pathological abnormalities were noted.

Aerosol Studies

Guinea Pigs 6 controls (and untreated) (saline) 72 experimentals 3% and 18% (Acetylcysteine) dosed for a total of 17 minutes, 2 minutes with spray 15 minutes in the chamber. One 3% and one 18% group was exposed for 8 weeks - mortality was 54% in 3% group and 42% in the 18% group. Mortality in the 8 week saline controls was 25%. Two 18% groups were sensitized and challenged, mortality was 38%; sensitized saline controls mortality 17%. In the untreated controls the mortality was 46%. Gross and Microscopic Pathology in the Guinea Pigs included only observation of tissues from the lungs, bronchi, trachea, and larynx.

Intracutaneous Irritation Guinea Pigs (pg. 1-52 NDA)

This study indicates that Acetylcysteine is a mild irritant at concentrations of approximately 8% and less.

Ciliary Activity Studies in Rats Trachae

Rat trachae were used in ciliary motility studies to indicate the cellular irritation of Acetylcysteine. Manufacturer concludes that the drug is non-irritating at a concentration of 3%.

Dermal Irritation in Rabbits (Vol. 1, pg. 55)

4 x 4 inch area of abdominal skin exposed to a 3% solution of Acetylcysteine for 20 exposures 17 hours per exposure produced no significant irritation except for one rabbit which exhibited an acute localized reaction. 10 rabbits were used. Saline produced "a diffuse - moderate to marked - acute inflammatory reaction with minimal focal subacute chronic inflammation." Microscopic examination of the skin of the animals on 3% Acetylcysteine solution revealed no diffuse acute irritation reaction. In the control animals (normal saline) there was a generalized diffuse acute inflammatory reaction with polymorphonuclear all infiltrate edema and congestion involving papillary layer of the skin generally.

Guinea Pig Respiratory Mucosa Sensitization

There was no evidence of sensitization grossly after a regimen of 3 weeks (15 exposures) of aerosol exposure rested two weeks and three (3 days) of consecutive exposures. (Each exposure was 2 minutes of aerosol and 15 minutes in the chamber) The concentration of acetylcysteine was 10%. Microscopic pathology revealed that 2 of 8 animals had grossly consolidated, extensive, diffuse, confluent chronic, organizing and acute bronchopneumonia.

Sensitization of Skin by Aerosol Exposure in Guinea Pigs

No reported sensitization of the skin by aerosol exposure.

Sensitization of Guinea Pigs by I.P. Administration

The results indicate that no significant sensitivity to acetylcysteine in guinea pigs when administered intraperitoneally and challenged with an I.V. dose after a three week rest period.

Pharmacodynamic Studies

Effect of Acetylcysteine on the action of Phenylephrine on smooth muscle of the Rat

Studies indicate that there is no potentiative effect of phenylephrine in one of the formulations with acetylcysteine as compared to phenylephrine in normal saline in rat smooth muscle.

Evaluation - Inadequate (animal studies)

1. Aerosol Studies in Guinea Pigs were inadequate to prove safety over prolonged period. A high mortality rate was noted in both control and treated animals. Microscopic pathology and gross pathology showed a significant number of lesions. More than one specie of animal should be used.

Chronic toxicity as well as acute toxicity studies should be done.

2. Ciliary motility in the Rats, according to data, do not indicate to this reviewer that irritancy is due to action of cetylpyridinium chloride, as manufacturer claims.

3. Dermal irritation data indicate that the drug is non-irritating and that normal saline produces an acute localized inflammatory reaction. This is a first for saline!

4. Sensitization of skin by aerosol exposure in guinea pigs is a method by which skin sensitization is not generally produced except in the case of severe chemical sensitizers.

5. Sensitization of Guinea Pigs by I.P. administration of acetylcysteine appears to be a method for demonstrating cumulative toxicity rather than a sensitization (as the manufacturer claims).

A brief review of the clinical records indicate that there are no adverse reactions or side effects to this drug.

From the clinical records of this drug and from in vitro studies it is evident that H_2S is released from the action of the drug. H_2S is known to produce symptoms of toxicity in concentrations of 1:200,000. (Sollman 8th Ed.) Since this drug site of action is in the lungs, it is our opinion that studies should be done to demonstrate whether or not this is a point of safety.

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cc: NDA 13-601 (orig. & 2cc)
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