



August 11, 2000

VIA Fax: 301.827.5562 and Fed-Ex

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**Attention: Ms. Andrea C. Masci**  
Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5600 Fishers Lane, Rm. 1061  
ROCKVILLE MD 20852

Dear Ms. Masci:

**DOCKET NO: 00N-1357**

We hereby request Methacholine Chloride USP be identified by regulation, as a drug product that "presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product."

Under section 503A of the Act, a compounded drug product is a drug product made in response or in anticipation of, receipt of a valid prescription order or a notation on a valid prescription order from a licensed practitioner that states the compounded product is necessary for the identified patient.

In our opinion, compounding of bulk chemical Methacholine Chloride USP affects the potency, purity, and quality of this drug product. Due to the drug product's hygroscopic characteristic, there is significant potential for error in one or more of the steps that could affect drug safety and effectiveness. Studies show that the weighing process should be done within a low relative humidity environment, below 15%. During the weighing process, a hygroscopic powder absorbs moisture thereby affecting the weight and strength of the product administered to the patient.

The potential for contamination is also a factor when considering the handling of bulk material. FDA recognizes that the drug product has tendencies to have microbial contamination and therefore demands microbiological tests for the pharmaceutical grade drug product. Our product Provocholine® NDC #64281-100-06/12 is controlled and tested according to cGMP conditions and FDA regulations. Impurities can not exceed 0.1%. The drug product made with chemicals and sold in bulk for compounding is not required to have microbiological tests and may be contaminated. Lack of consistent testing on the bulk material may result in questionable safety and efficacy issues regarding the product when there is product to product variability.

Due to the above reasons and in accordance with Section 503A of the Act, we request that you include Methacholine Chloride USP bulk on your list of products that can not be compounded.

Sincerely,

  
Sally Ilene Fernbach  
Operations Manager

fc: Victor Guimaraes, V.P. Regulatory Affairs  
Luciano Calenti, President

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Attachment - Provocholine® Product Insert

00N-1357

cb  


# PROVOCHOLINE®

brand of  
methacholine chloride  
POWDER FOR INHALATION  
NOT FOR INJECTION

PROVOCHOLINE® (METHACHOLINE CHLORIDE POWDER FOR INHALATION) IS A BRONCHOCONSTRICTOR AGENT FOR DIAGNOSTIC PURPOSES ONLY AND SHOULD NOT BE USED AS A THERAPEUTIC AGENT. PROVOCHOLINE® (METHACHOLINE CHLORIDE POWDER FOR INHALATION) INHALATION CHALLENGE SHOULD BE PERFORMED ONLY UNDER THE SUPERVISION OF A PHYSICIAN TRAINED IN AND THOROUGHLY FAMILIAR WITH ALL ASPECTS OF THE TECHNIQUE OF METHACHOLINE CHALLENGE, ALL CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, AND THE MANAGEMENT OF RESPIRATORY DISTRESS.

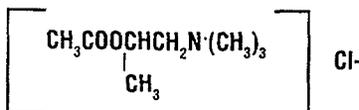
EMERGENCY EQUIPMENT AND MEDICATION SHOULD BE IMMEDIATELY AVAILABLE TO TREAT ACUTE RESPIRATORY DISTRESS.

PROVOCHOLINE (METHACHOLINE CHLORIDE POWDER FOR INHALATION) SHOULD BE ADMINISTERED ONLY BY INHALATION. SEVERE BRONCHOCONSTRICTION AND REDUCTION IN RESPIRATORY FUNCTION CAN RESULT FROM THE ADMINISTRATION OF PROVOCHOLINE (METHACHOLINE CHLORIDE POWDER FOR INHALATION). PATIENTS WITH SEVERE HYPERREACTIVITY OF THE AIRWAYS CAN EXPERIENCE BRONCHOCONSTRICTION AT A DOSAGE AS LOW AS 0.025 MG/ML (0.125 CUMULATIVE UNITS). IF SEVERE BRONCHOCONSTRICTION OCCURS, IT SHOULD BE REVERSED IMMEDIATELY BY THE ADMINISTRATION OF A RAPID-ACTING INHALED BRONCHODILATOR AGENT (BETA AGONIST). BECAUSE OF THE POTENTIAL FOR SEVERE BRONCHOCONSTRICTION, PROVOCHOLINE (METHACHOLINE CHLORIDE POWDER FOR INHALATION) CHALLENGE SHOULD NOT BE PERFORMED IN ANY PATIENT WITH CLINICALLY APPARENT ASTHMA, WHEEZING, OR VERY LOW BASELINE PULMONARY FUNCTION TESTS (E.G., FEV<sub>1</sub> LESS THAN 1 TO 1.5 LITER OR LESS THAN 70% OF THE PREDICTED VALUES). PLEASE CONSULT STANDARD NOMOGRAMS FOR PREDICTED VALUES.

**DESCRIPTION:** Provocholine® (methacholine chloride powder for inhalation) is a parasympathomimetic (cholinergic) broncho-constrictor agent to be administered in solution only, by inhalation, for diagnostic purposes. Each 20 mL vial contains 100 mg of methacholine chloride powder which is to be reconstituted with 0.9% sodium chloride injection containing 0.4% phenol (pH 7.0). See DOSAGE AND ADMINIS-

TRATION for dilution procedures, concentrations and schedule of administration.

Chemically, methacholine chloride (the active ingredient) is 1-propanaminium, 2-(acetyloxy)-N,N,N-trimethyl-chloride. It is a white to practically white deliquescent compound, soluble in water. Methacholine chloride has an empirical formula of C<sub>9</sub>H<sub>8</sub>ClNO<sub>2</sub>, a calculated molecular weight of 195.69, and the following structural formula:



**CLINICAL PHARMACOLOGY:** Methacholine chloride is the β-methyl homolog of acetylcholine and differs from the latter primarily in its greater duration and selectivity of action. Bronchial smooth muscle contains significant parasympathetic (cholinergic) innervation.

Bronchoconstriction occurs when the vagus nerve is stimulated and acetylcholine is released from the nerve endings. Muscle constriction is essentially confined to the local site of release because acetylcholine is rapidly inactivated by acetylcholinesterase.

Compared with acetylcholine, methacholine chloride is more slowly hydrolyzed by acetylcholinesterase and is almost totally resistant to inactivation by nonspecific cholinesterase or pseudocholinesterase.

When a sodium chloride solution containing methacholine chloride is inhaled, subjects with asthma are markedly more sensitive to methacholine-induced bronchoconstriction than are healthy subjects. This difference in response is the pharmacologic basis for the Provocholine® (methacholine chloride powder for inhalation) inhalation diagnostic challenge. However, it should be recognized that methacholine challenge may occasionally be positive after influenza, upper respiratory infections or immunizations, in very young or very old patients, or in patients with chronic lung disease (cystic fibrosis, sarcoidosis, tuberculosis, chronic obstructive pulmonary disease). The challenge may also be positive in patients with allergic rhinitis without asthma, in smokers, in patients after exposure to air pollutants, or in patients who have had or will in the future develop asthma.

There are no metabolic and pharmacokinetic data available on methacholine chloride.

**INDICATIONS AND USAGE:** Provocholine® (methacholine chloride powder for inhalation) is indicated for the diagnosis of bronchial airway hyperreactivity in subjects who do not have clinically apparent asthma.

**CONTRAINDICATIONS:** Provocholine® (methacholine chloride powder for inhalation) is contraindicated in patients with known hypersensitivity to this drug or to other parasympathomimetic agents.

Repeated administration of Provocholine® (methacholine chloride powder for inhalation) by inhalation other than on the day that a patient undergoes challenge with increasing doses is contraindicated.

Inhalation challenge should not be performed in patients receiving any beta-adrenergic blocking agent because in such patients responses to methacholine chloride can be exaggerated or prolonged, and may not respond as readily to accepted modalities of treatment (see WARNINGS box).

**PRECAUTIONS: General:** Administration of Provocholine® (methacholine chloride powder for inhalation) to patients with epilepsy, cardiovascular disease accompanied by bradycardia, vagotonia, peptic ulcer disease, thyroid disease, urinary tract obstruction or other

condition that could be adversely affected by a cholinergic agent should be undertaken only if the physician feels benefit to the individual outweighs the potential risks.

**Information for Patients:** To assure the safe and effective use of Provocholine® (methacholine chloride powder for inhalation) inhalation challenge, the following instructions and information should be given to patients:

1. Patients should be instructed regarding symptoms that may occur as a result of the test and how such symptoms can be managed.
2. A female patient should inform her physician if she is pregnant, or the date of her last onset of menses, or the date and result of her last pregnancy test. (See PRECAUTIONS: Pregnancy.)

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** There have been no studies with methacholine chloride that would permit an evaluation of its carcinogenic or mutagenic potential or of its effect on fertility.

**Pregnancy:** Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with methacholine chloride. It is not known whether methacholine chloride can cause fetal harm when administered to a pregnant patient or affect reproductive capacity. Methacholine chloride should be given to a pregnant woman only if clearly needed.

**IN FEMALES OF CHILDBEARING POTENTIAL, PROVOCHOLINE® (METHACHOLINE CHLORIDE POWDER FOR INHALATION) INHALATION CHALLENGE SHOULD BE PERFORMED EITHER WITHIN TEN DAYS FOLLOWING THE ONSET OF MENSES OR WITHIN 2 WEEKS OF A NEGATIVE PREGNANCY TEST.**

**Nursing Mothers:** Provocholine® (methacholine chloride powder for inhalation) inhalation challenge should not be administered to a nursing mother since it is not known whether methacholine chloride when inhaled is excreted in breast milk.

**Pediatric Use:** The safety and efficacy of Provocholine® (methacholine chloride powder for inhalation) inhalation challenge have not been established in children below the age of 5 years.

**ADVERSE REACTIONS:** Adverse reactions associated with 153 inhaled methacholine chloride challenges include one occurrence each of headache, throat irritation, lightheadedness and itching.

Provocholine® (methacholine chloride powder for inhalation) is to be administered only by inhalation. When administered orally or by injection, methacholine chloride is reported to be associated with nausea and vomiting, substernal pain or pressure, hypotension, fainting and transient complete heart block. (See OVERDOSAGE.)

**OVERDOSAGE:** Provocholine® (methacholine chloride powder for inhalation) is to be administered only by inhalation. When administered orally or by injection, overdosage with methacholine chloride can result in a syncope reaction, with cardiac arrest and loss of consciousness. Serious toxic reactions should be treated with 0.5 mg to 1 mg of atropine sulfate, administered IM or IV.

The acute (24-hour) oral LD<sub>50</sub> of methacholine chloride and related compounds is 1100 mg/kg in the mouse and 750 mg/kg in the rat.

Cynomolgus monkeys were exposed to a 2% (20 mg/mL) aerosol of methacholine chloride in acute (10-minute) and subchronic (7-day) inhalation toxicity studies. In the former study, animals exposed to the aerosol

for up to 10 minutes demonstrated an increase in respiratory rate and decrease in tidal volume after 30 seconds. These changes peaked at 2 minutes and were followed by a rise in pulmonary resistance and a decrease in compliance. Pulmonary function returned to normal 20 to 25 minutes after exposure ended. In the 7-day study, monkeys were given daily inhalations equivalent to the maximum and roughly five times the maximum standard human dose. Although the typical pulmonary response/recovery sequence was observed, distinct changes in airway resistance were noted at the end of the study. These changes were not rapidly reversed in the maximum equivalent standard-dose group, which was observed for 9 weeks.

**DOSAGE AND ADMINISTRATION:** Before Provocholine® (methacholine chloride powder for inhalation) inhalation challenge is begun, baseline pulmonary function tests must be performed. A subject to be challenged must have an FEV<sub>1</sub> of at least 70% of the predicted value.

The target level for a positive challenge is a 20% reduction in the FEV<sub>1</sub>, compared with the baseline value after inhalation of the control sodium chloride solution. This target value should be calculated and recorded before Provocholine® (methacholine chloride powder for inhalation) challenge is started.

**Dilutions:** (Note: Do not inhale powder. Do not handle this material if you have asthma or hay fever.) All dilutions should be made with 0.9% sodium chloride injection containing 0.4% phenol (pH 7.0) using sterile, empty USP Type I borosilicate glass vials. After adding the sodium chloride solution, shake each vial to obtain a clear solution.

**DILUTION SEQUENCE-MULTIPLE PATIENT TESTING (2-5 PATIENTS)**

[REQUIRES 2 VIALS OF PROVOCHOLINE® (methacholine chloride powder for inhalation)]

Vials		Concentrations
A <sub>1</sub> & A <sub>2</sub>	Add 4 mL of 0.9% sodium chloride injection containing 0.4% phenol (pH 7.0) to each of two 20 mL vials containing 100 mg of Provocholine® (methacholine chloride powder for inhalation). These will be designated vials A <sub>1</sub> and A <sub>2</sub> .	25 mg/mL
B	Remove 3 mL from vial A <sub>1</sub> , transfer to another vial and add 4.5 mL of 0.9% sodium chloride injection containing 0.4% phenol (pH 7.0). This is vial B.	10 mg/mL
C	Remove 1 mL from vial A <sub>2</sub> , transfer to another vial and add 9 mL of 0.9% sodium chloride injection containing 0.4% phenol (pH 7.0). This is vial C.	2.5 mg/mL
D	Remove 1 mL from vial C, transfer to another vial and add 9 mL of 0.9% sodium chloride injection containing 0.4% phenol (pH 7.0). This is vial D.	0.25 mg/mL
E	Remove 1 mL from vial D, transfer to another vial and add 9 mL of 0.9% sodium chloride injection containing 0.4% phenol (pH 7.0). This is vial E. Vial E must be prepared on the day of challenge.	0.025 mg/mL

**DILUTION SEQUENCE-SINGLE PATIENT TESTING**

Vials		Concentrations
A	Add 4 mL of 0.9% sodium chloride injection containing 0.4% phenol (pH 7.0) to the 20 mL vial containing 100 mg of Provocholine® (methacholine chloride powder for inhalation). This is vial A.	25 mg/mL
B	Remove 1 mL from vial A, transfer to another vial and add 1.5 mL of 0.9% sodium chloride injection containing 0.4% phenol (pH 7.0). This is vial B.	10 mg/mL
C	Remove 1 mL from vial A, transfer to another vial and add 9 mL of 0.9% sodium chloride injection containing 0.4% phenol (pH 7.0). This is vial C.	2.5 mg/mL
D	Remove 1 mL from vial C, transfer to another vial and add 9 mL of 0.9% sodium chloride injection containing 0.4% phenol (pH 7.0). This is vial D.	0.25 mg/mL
E	Remove 1 mL from vial D, transfer to another vial and add 9 mL of 0.9% sodium chloride injection containing 0.4% phenol (pH 7.0). This is vial E. Vial E must be prepared on the day of the challenge.	0.025 mg/mL

Dilutions A through D should be stored at 36° to 46°F (2° to 8°C) in a refrigerator and can be stored for not more than 2 weeks. [The unreconstituted powder should be stored at 59°F to 86°F (15° to 30°C)]. After this time, discard the vials and prepare new dilutions. Freezing does not affect the stability of dilutions A through D. Vial E must be prepared on the day of challenge.

**A sterile bacterial-retentive filter (porosity 0.22 µm should be used when transferring a solution from each vial (at least 2 mL) to a nebulizer.**

**Procedure:** A standardized procedure for inhalation has been developed.

The challenge is performed by giving a subject ascending serial concentrations of Provocholine® (methacholine chloride powder for inhalation). At each concentration, five breaths are administered by a nebulizer that permits intermittent delivery time of 0.6 seconds by a breath-actuated timing device (dosimeter).

At each of five inhalations of a serial concentration, the subject begins at functional residual capacity (FRC) and slowly and completely inhales the dose delivered. Within 5 minutes, FEV<sub>1</sub> values are determined. The procedure ends either when there is a 20% or greater reduction in the FEV<sub>1</sub>, compared with the baseline sodium chloride solution value (ie, a positive response) or if 188.88 total cumulative units has been administered (see table below) and the FEV<sub>1</sub> has been reduced by 14% or less (ie, a negative response). If there is a reduction of 15% to 19% in the FEV<sub>1</sub>, compared with baseline, either the challenge may be repeated at that concentration or a higher concentration may be given as long as the dosage administered does not result in total cumulative units exceeding 188.88.

The following is a suggested schedule for the administration of Provocholine® (methacholine chloride powder for inhalation) challenge. Cumulative units are calculated by multiplying the number of breaths by the concentration administered.

Total cumulative units is the sum of cumulative units for each concentration administered.

Serial Concentration	Number of Breaths	Cumulative Units per Concentration	Total Cumulative Units
0.025 mg/mL	5	0.125	0.125
0.25 mg/mL	5	1.25	1.375
2.5 mg/mL	5	12.5	13.88
10.0 mg/mL	5	50.0	63.88
25.0 mg/mL	5	125.0	188.88

An inhaled beta-agonist may be administered after Provocholine® (methacholine chloride powder for inhalation) challenge to expedite the return of the FEV<sub>1</sub> to baseline and to relieve the discomfort of the subject. Most patients revert to normal pulmonary function within 5 minutes following bronchodilators or within 30 to 45 minutes without any bronchodilator.

**HOW SUPPLIED:** 20-mL amber vials containing 100 mg of methacholine chloride powder which is to be reconstituted with 0.9% sodium chloride injection containing 0.4% phenol (pH 7.0) - boxes of 12 (NDC 64281-100-12) or boxes of 6 (NDC 64281-100-06). Store the powder at 59° to 86°F (15° to 30°C). Refrigerate the reconstituted solutions (dilutions A-D) at 36° to 46°F (2° to 8°C) for not more than 2 weeks. Dilution E must be prepared on the day of the challenge.

**REFERENCE:** 1. Morris JF, Koski WA, Johnson LC. Spirometric standards for healthy non-smoking adults. *Am Rev Resp Dis.* Jan 1971; 103: 57-67.

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