

Attachment 2

Proposed Provocholine[®] Labeling 1280 mg/vial

Methacholine Chloride

POWDER FOR INHALATION

NOT FOR INJECTION

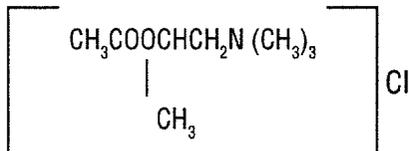
METHACHOLINE CHLORIDE POWDER FOR INHALATION IS A BRONCHOCONSTRICTOR AGENT FOR DIAGNOSTIC PURPOSES ONLY AND SHOULD NOT BE USED AS A THERAPEUTIC AGENT. METHACHOLINE CHLORIDE INHALATION CHALLENGE SHOULD BE PERFORMED ONLY UNDER THE SUPERVISION OF A PHYSICIAN TRAINED IN AND THOROUGHLY FAMILIAR WITH ALL ASPECTS 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.

METHACHOLINE CHLORIDE SHOULD BE ADMINISTERED ONLY BY INHALATION. SEVERE BRONCHOCONSTRICTION AND REDUCTION IN RESPIRATORY FUNCTION CAN RESULT FROM THE ADMINISTRATION OF METHACHOLINE CHLORIDE. 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, METHACHOLINE CHLORIDE CHALLENGE SHOULD NOT BE PERFORMED IN ANY PATIENT WITH CLINICALLY APPARENT ASTHMA, WHEEZING, OR VERY LOW BASELINE PULMONARY FUNCTION TESTS (e.g., FEV₁ LESS THAN 1 TO 1.5 LITER OR LESS THAN 70% OF THE PREDICTED VALUES). PLEASE CONSULT STANDARD NOMOGRAMS FOR PREDICTED VALUES.¹

DESCRIPTION: Methacholine Chloride powder for inhalation is a parasympathomimetic (cholinergic) bronchoconstrictor agent to be administered in solution only, by inhalation, for diagnostic purposes. Each 20 mL vial contains 1280 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 ADMINISTRATION 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 C₉H₁₈ClNO₂, 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 pseudoacetylcholinesterase.

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 methacholine chloride powder for inhalation 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: Methacholine Chloride powder for inhalation is indicated for the diagnosis of bronchial airway hyperreactivity in subjects who do not have clinically apparent asthma.

CONTRAINDICATIONS: Methacholine Chloride powder for inhalation is contraindicated in patients with known hypersensitivity to this drug or to other parasympathomimetic agents.

Repeated administration of Methacholine Chloride 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 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 Methacholine Chloride 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, METHACHOLINE CHLORIDE 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: Methacholine Chloride 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 Methacholine Chloride inhalation challenge have not been established in children below the age of 5 years.

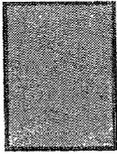
ADVERSE REACTIONS: Adverse reactions associated with 153 inhaled methacholine chloride challenges include one occurrence each of headache, throat irritation, lightheadedness and itching.

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: Methacholine Chloride powder for inhalation is to be administered only by inhalation. When administered orally or by injection, overdose with methacholine chloride can result in a syncopal 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 LD₅₀ 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



Orange 021 PMS 3302 Pattern Varnish

Contains 6 x 20 mL containers

Exp. Lot No.

For Oral Inhalation Only
NDC XXXX-XX-XX

Methacholine Chloride
Powder For Inhalation
1280 mg

WARNING: Not for Injection.

MFG. by Pancap for
Delbapharm inc.
Brantford, Ontario, Canada N3T 2V6

Rx Only

The vial contains 1280 mg Methacholine Chloride USP powder for the preparation of stock solution and dilutions. A sterile bacterial-retentive filter (porosity 0.22µm) should be used when transferring a solution from each vial (at least 2 mL) to a nebulizer. For use as a challenge test, under physician's supervision only. Storage: Store powder at 59 to 86 F. Refrigerate solutions at 36 to 46F. **IMPORTANT:** For directions, warnings and other important use information, read accompanying insert. 76X299 R3

20 mL size container

For Oral Inhalation Only
NDC XXXX-XX-XX

Methacholine Chloride
Powder For Inhalation
1280 mg

WARNING: Not for Injection.

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Delbapharm inc.
Brantford, Ontario, Canada N3T 2V6

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Lot No.
Exp.

Contains 12 x 20 mL containers

Exp. Lot No.

For Oral Inhalation Only
NDC XXXX-XX-XX

Methacholine Chloride
Powder For Inhalation
1280 mg

WARNING: Not for Injection.

MFG. by Pancap for
Delbapharm inc.
Brantford, Ontario, Canada N3T 2V6

Rx Only

The vial contains 1280 mg Methacholine Chloride USP powder for the preparation of stock solution and dilutions. A sterile bacterial-retentive filter (porosity 0.22µm) should be used when transferring a solution from each vial (at least 2 mL) to a nebulizer. For use as a challenge test, under physician's supervision only. Storage: Store powder at 59 to 86 F. Refrigerate solutions at 36 to 46F. **IMPORTANT:** For directions, warnings and other important use information, read accompanying insert. 76X299 R3



Orange 021 PMS 3302 Pattern Varnish

